

APPENDIX A

REVIEWS AND TIER ASSIGNMENTS FOR EPIDEMIOLOGIC STUDIES OF ETS AND LUNG CANCER

APPENDIX A. REVIEWS AND TIER ASSIGNMENTS FOR EPIDEMIOLOGIC STUDIES OF ETS AND LUNG CANCER

A.1. INTRODUCTION

This appendix contains material that is used in Section 5.5, entitled *Analysis by Tier and Country*. As described in that section, each study is individually reviewed and assigned to one of four tiers based on its assessed utility for the objective of evaluating the evidence of an association between environmental tobacco smoke (ETS) exposure and incidence of lung cancer. The means of constructing study reviews is described in the next section, followed by a description of the scheme for scoring studies on various items and then assigning the studies to tiers according to the outcome. The final section of this appendix contains the individual study reviews and the tier numbers assigned to them.

A.2. CONSTRUCTION OF INDIVIDUAL STUDY REVIEWS

Descriptions of the four prospective cohort studies are individualized according to the requirements of each study. Reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study form designed around principles of good epidemiologic practice and issues specific to environmental tobacco smoke; and (3) a section of comments related to evaluation and interpretation of the study. The study reviews are used to assign studies to tiers according to the procedure described in Section A.3.

The review form for case-control studies shown in Section A.2.1 was completed for each case-control study in order to systematically extract information about characteristics of interest for preparation of the reviews. The form was an aid in treating study reviews uniformly and noting omissions or incomplete discussion on issues that may affect the potential for bias or confounding.

The study descriptions in Section A.4 were then prepared by following the outline and information in the completed forms. Some items included in the form pertain to characteristics that would apply to a case-control study on any topic, i.e., they are "generic items" related to principles of good epidemiologic investigation; the remaining items tend to identify areas of potential bias specific to the topic of ETS and lung cancer.

A.2.1. Review Form for Case Control Studies

PART I. GENERAL

Study name _____

Location _____
Time period (data collection) _____

Study objective(s) _____

_____ The

source of the primary data set is the current study _____ or a parent study

(ref) _____

_____ containing CS (current) _____ FS (former) _____ NS (never-smoker) _____

Study uses term "nonsmoker" _____ or "never-smoker" _____ to mean

nonsmoker _____

_____ never-smoker _____

"Exposed" to ETS means (preferably in terms of spousal smoking)

Recall span (how far back in time ETS exposure was measured) _____

ETS sources include cigarette _____ cigar _____ pipe _____ other _____

Describe inclusion of nonsmoking (never-smoking) females not currently married (number of cases and controls, assumptions regarding exposure)

II. DATA COLLECTION (includes NS_____ FS_____ CS_____ unless noted)

Inclusion/exclusion criteria

Cases_____

Controls (include matching variables in PART V)_____

Main source of subjects Cases Controls

Hospital(s) # _____

Community _____

Other _____

Incident cases Y_____ N_____

Control sampling

Cumulative _____ Density _____

Unmatched _____ Matched _____

Method of collection Cases Controls

Face-to-face _____

Telephone _____

Self-admin. ques. _____

Medical records _____

Vital stat. records _____

Other _____

Collected data verified/corroborated with other sources Y_____ N_____

Cases

Controls

Sample size
(prior to attrition)

females _____

males _____

Attrition
(selection or followup)

females	_____	_____	
males	_____	_____	
Source of response			
subject	_____	_____	
proxy	_____	_____	
Exposure sources	NS_____ FS_____ CS_____		
	<u>Yes</u>	<u>No</u>	
Childhood	_____	_____	
Adulthood	_____	_____	
Spouse	_____	_____	
Parents/in-laws	_____	_____	
Other family/	_____	_____	
live-ins			
Workplace	_____	_____	
Other	_____	_____	
Age	NS_____ FS_____ CS_____		
	<u>Distribution</u>	<u>Cases</u>	<u>Controls</u>
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
Mean		_____	_____
Standard error		_____	_____
Standard deviation		_____	_____
Range		_____	_____

PART III. CLINICAL DATA

<u>Primary</u> lung cancer verified by	NS_____ FS_____ CS_____
Histology	_____
Cytology	_____
Radiology/clinical	_____
Death certificate	_____
Tumor registry	_____
Mortality records	_____

Other _____
Not verified _____
 Airway proximity (no. exp cases/no. cases) NS____ FS____ CS____

Central _____
 Table_____
 Peripheral _____

Tumor type (no. exp cases/no. cases) NS____ FS____ CS____
 Squamous cell _____
 Table_____
 Small cell _____
 Adenocarcinoma _____
 Large cell _____
 Others or unspecified _____

PART IV. STATISTICAL ANALYSIS (includes NS____ FS____ CS____ unless noted)

Raw data (for analysis)	<u>Cases</u>	<u>Controls</u>
females unexp	_____	_____
exp	_____	_____
males unexp	_____	_____
exp	_____	_____

Comments (include measure of exposure) Table _____

Unadjusted (crude) analysis

Estimate OR _____ % CI (_____, _____)

Comments Table _____

Test of p-value _____
 signif.

Test for p-value _____
 trend

Comments Table _____

Adjusted analysis

Estimate OR _____ % CI (_____,_____)

Test of p-value _____
signif.

Test for
trend p-value _____

Comments

Table _____

PART V. DEPENDENT VARIABLES (potential confounders and effects modifiers considered)

	<u>In Matching</u>	<u>In Analysis</u>	<u>Otherwise</u>
Age	_____	_____	_____
Gender	_____	_____	_____
Race/ethnicity	_____	_____	_____
Hospital	_____	_____	_____
Residence/ neighborhood	_____	_____	_____
Housing type	_____	_____	_____
House/room sizes	_____	_____	_____
Vital statistics	_____	_____	_____
Smoking status	_____	_____	_____
SES	_____	_____	_____
Medical health	_____	_____	_____
Menstrual/ reproductive	_____	_____	_____
Occupation	_____	_____	_____
Outdoor air pollution	_____	_____	_____
Cooking habits	_____	_____	_____
Drinking	_____	_____	_____
Diet	_____	_____	_____
Education	_____	_____	_____
Family history of lung cancer	_____	_____	_____
Other indoor smoke/fumes	_____	_____	_____
Radon	_____	_____	_____
Lifestyle	_____	_____	_____
Climate/ ventilation	_____	_____	_____

A.3. TIER CLASSIFICATION SCHEME

The items and study scores used in the algorithm to calculate tier numbers are given in Table A-1. The items and scoring system in that table and the algorithm for converting the scores to a tier number are the topics of this section.

The items displayed in the headings of Table A-1 will be described after explanation of how assignments are calculated from the numbers in that table. Positive values in the table are unfavorable (penalty points); a blank entry means the item was not a problem; negative values are favorable (bonus points) and occur in a few instances where

the study performed well above the norm indicated by a blank, e.g., FONT, KOO, and HOLE(Coh) each have an entry of "-0.5" under "Less than 90% confirmation by histology or cytology" in Category C for particularly high attention given to confirming primary lung cancer in subjects classified as cases. Bonus scores are always -0.5 and are assigned somewhat sparingly as they have the potential to cancel penalty scores and thus mask a study weakness. Parentheses around an entry indicate that the penalty points were assigned due to insufficient information (so there is effectively a penalty imposed if the information needed was not included in the source). The asterisk that occurs under the item "unsuitable indoor environment" is a marker that automatically places the study into Tier 4 under the assignment rule to be described next (the unsuitable environment refers to high levels of coal smoke in all instances).

Tier numbers for each study are calculated from the entries in Table A-1 as follows. Totals are calculated by category and across all items, as shown in Table A-2. If the total for each category is less than 2.5, then the tier assignment is determined as follows:

<u>Total Score</u>	<u>Tier</u>
1.75 or less	1
2.00 - 3.75	2
4.00 - 5.75	3
6.00 or greater	4

The value 2.5 is designated as a cutoff point for each category. If a study has one or more category totals greater than or equal to 2.5, the tier classification is increased by 1 (i.e., 1 is added to the tier number shown in the above table if any category totals are 2.5 or greater). The three studies conducted in regions of China where indoor air is heavily polluted with smoke from burning coal, denoted by an asterisk under item "unsuitable indoor environment," are placed in Tier 4 (see reviews in Section A.4 for GENG, LIU, and WUWI). The resultant assignment of studies to tiers is shown in Table A-2.

A scheme that attempts to assess utility and to numerically rank studies accordingly, as done here, has a high degree of subjectivity. Different analysts would be apt to disagree about elements of any such approach and the appropriate weights for those elements in assigning studies to tiers, as suggested above. One of the difficulties is that the significance of a study "weakness" is difficult to assess. For example, the use of proxy respondents may be a source of bias, but the direction and magnitude of bias are unknown for any given study. Thus, one is faced with rating studies largely on the basis of one's ability to ascertain what study features are significant and

Table A-1. Study scores for tier assignments

Study	Category A		Category B		
	Former smokers included	Smoking status unverified	Exposure criteria questionable	Exposure of unmarrieds	Exposure status unverified
AKIB					-0.5
BROW			1	(0.5)	
BUFF			1.5		
CHAN			2	(0.5)	
CORR				0.5	
FONT		-0.5			-0.5
GAO			1.5	0.5	
GARF			0.5	0.5	
GENG	1		1		
HUMB	0.5				
INOUE	1		1		
JANE					
KABA	0.5		1		
KALA					
KOO					
LAMT	0.5				
LAMW					
LEE					
LIU			1		
PERS		-0.5			
SHIM					
SOBU					
SVEN					
TRIC	1				
WU				0.5	
WUWI	1				
BUTL(Coh)					
GARF(Coh)			1		

WU		0.5
WUWI	1	
HIRA(Coh)	0.5	
HOLE(Coh)		

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Table A-1. (continued)

Study	Category C		Category D	
	Secondary lung cancers possible	Less than 90% confirm. histol./cytol.	Less than 90% face-to-face	Unblinded interviews
AKIB		1	0.5	
BROW				
BUFF				
CHAN	0.75	0.5		
CORR				(0.5)
FONT		-0.5		(0.5)
GAO		0.5		(0.5)
GARF				
GENG				
HUMB		0.5		
INOUE	0.75	(0.5)		(0.5)
JANE				0.5
KABA				
KALA		0.5		(0.5)
KOO		-0.5		
LAMT				
LAMW				(0.5)
LEE	0.75	(0.5)		0.5
LIU	0.75	1		
PERS			0.5	
SHIM			0.5	(0.5)
SOBU			0.5	(0.5)
SVEN			1	0.5
TRIC		1		0.5
WU			1	0.5
WUWI		0.5		0.5
BUTL(Coh)			0.5	
GARF(Coh)	0.5	1	0.5	

WU			1	0.5
WUWI		0.5		0.5
HIRA(Coh)	(0.5)	0.5		
HOLE(Coh)	(0.5)	-0.5		

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Table A-1. (continued)

Study	Category E		Category F	
	More than 10% proxy respondents	Uneven proxy response distribution	Change in smoking or ETS status	(Cohort Only) More than 10% loss to followup
AKIB	1			
BROW	1	0.75		
BUFF	1			
CHAN	0.75			
CORR	0.5			
FONT	0.5			
GAO				
GARF	1.5			
GENG				
HUMB	1	0.75		
INOUE	1			
JANE	0.5			
KABA				
KALA				
KOO				
LAMT				
LAMW				
LEE	0.5			
LIU				
PERS	(0.5)			
SHIM				
SOBU				
SVEN				
TRIC				

WU		
WUWI		
BUTL(Coh)	0.5	
GARF(Coh)	0.5	0.75
HIRA(Coh)	0.5	
HOLE(Coh)	0.5	(0.5)

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Table A-1. (continued)

Study	Category G		
	(Case-control only)		
	Unsuitable indoor environment	Smoking-related disease in controls	Nonincident cases included
AKIB			0.5
BROW			(0.5)
BUFF			
CHAN		0.75	
CORR			0.5
FONT			
GAO			
GARF		0.75	(0.5)
GENG	*		
HUMB			
INOUE		0.75	(0.5)
JANE			
KABA			
KALA			
KOO			
LAMT			
LAMW			
LEE			
LIU	*		
PERS			
SHIM		0.75	(0.5)
SOBU		0.75	
SVEN		0.5	
TRIC			

WU	
WUWI	*
BUTL(Coh)	
GARF(Coh)	
HIRA(Coh)	
HOLE(Coh)	

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Table A-1. (continued)

Study	Category H		
	Uncontrolled for age	Uncontrolled for other factors	Problem(s) with stat. methods
AKIB			
BROW	1.5		0.5
BUFF	1.5		
CHAN	1.5		
CORR	1.5		
FONT		0.5	
GAO		1	
GARF			
GENG	1.5	1	
HUMB			
INOUE			
JANE			1
KABA	1.5		
KALA			
KOO			1
LAMT	1.5		
LAMW	1.5	1	
LEE			
LIU	1.5	1	
PERS			
SHIM	1.5		
SOBU		1	
SVEN			
TRIC	1.5		
WU			1
WUWI		1	
BUTL(Coh)		1	
GARF(Coh)			

WU		1
WUWI	1	
BUTL(Coh)	1	
HIRA(Coh)		
HOLE(Coh)		

Table A-2. Total scores and tier assignment

Study	Category								Total	Tier Assign.
	A	B	C	D	E	F	G	H		
AKIB		-0.5	1	0.5	1		0.5		2.5	2
BROW		1.5			1.75		0.5	2.0	5.75	3
BUFF		1.5			1			1.5	4.0	3
CHAN		2.5	1.25		0.75		0.75	1.5	6.75	4
CORR		0.5		0.5	0.5		0.5	1.5	3.5	2
FONT	-0.5	-0.5	-0.5	0.5	0.5			0.5	0	1
GAO		1.5	0.5	0.5				1.5	4.0	3
GARF		1			1.5		1.25		3.75	2
GENG	1	1					*	2.5	4.5	4
HUMB	0.5		0.5		1.75				2.75	2
INOUE	1	1	1.25	0.5	1		1.25		6.0	4
JANE				0.5	0.5			1	2.0	2
KABA	0.5	1						1.5	3.0	2
KALA			0.5	0.5					1.0	1
KOO			-0.5					1	0.5	1
LAMT	0.5							1.5	2.0	2
LAMW				0.5				2.5	3.0	3
LEE			1.25	0.5	0.5				2.25	2
LIU		1	1.75				*	2.5	5.25	4
PERS	-0.5			0.5	0.5				0.5	1
SHIM				1			1.25	1.5	3.75	2
SOBU				1			0.75	1	2.75	2
SVEN				1.5			0.5		2.0	2
TRIC	1		1	0.5				1.5	4.0	3
WU		0.5		1.5				1	3.0	2
WUWI	1		0.5	0.5			*	1	3.0	4
BUTL(Coh)				0.5		0.5		1	2.0	2
GARF(Coh)		1	1.5	0.5		1.25			4.25	3

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Table A-2. (continued)

Study	Category								Total	Tier Assign.
	A	B	C	D	E	F	G	H		
HIRA(Coh)	0.5		1			0.5			2.0	2
HOLE(Coh)						1			1.0	1

*Unsuitable indoor environment

some quantitative construct reflecting an opinion of their relative importance. Additionally, there is the possibility of misinterpreting the source or of the omission of needed information from the source. A further limitation is the inability to include all features of all studies that might affect one's judgment of it.

Reservations notwithstanding, the heterogeneity of the ETS studies in objectives and characteristics of design, data collection, analysis, and interpretation make it worthwhile to classify studies according to some evaluation of their utility for assessing ETS and lung cancer. The items used for scoring studies are described in the remainder of this section. The descriptions are written in the language of case-control studies (references to "cases," "controls," etc.). Where cohort studies are evaluated (end of Table A-1), the equivalent concept for cohort studies is applied under each category heading, with exceptions as noted in the text. An "ideal" is described for each item, to give the scores a reference point. The ideal applies to the needs of this report, however, and not to what may have been the ideal for the individual study objectives.

Very few of the studies were designed and executed with the sole, or even primary, objective of this report. Consequently, high penalty scores or an unfavorable tier assignment indicating limited utility for our objectives should not be interpreted as low study quality relative to the purpose for which the study was conducted. Comments included on the likely direction of bias refer to bias of the relative risk estimate. "Upward bias" is an expected excess in the observed relative risk above its true (but unknown) value (which is 1.0 if the null hypothesis of no effect is correct). "Downward bias" refers to bias in the opposite direction. "Bias toward the null hypothesis" is used sometimes in the text. It refers to an influence on the observed relative risk toward 1.0, the value of the true relative risk when the null hypothesis is correct. When the true relative risk exceeds 1, "bias toward the null" and "downward bias" are interchangeable. The probable magnitude of bias is more difficult to ascertain than the likely direction of bias. The relative values of the penalty scores under items in Table A-1 reflect our judgment on this issue. To determine why a specific study was scored with penalty or bonus points on any particular item, the reader needs to refer to the review of that study in Section A.4. A description of items in Table A-1 follows.

Category A: Never-Smoker Status

- Inclusion of former smokers. The ideal is for all subjects to be true never-smokers. Inclusion of subjects who report themselves as never-smokers but who are actually current smokers causes an upward bias in the relative risk (see Section 5.2.2 and Appendix B). Inclusion of former smokers may be a source of upward bias by similar arguments. Some degree of former smoking may be inconsequential depending on how much was smoked and the subsequent duration of abstinence, but this relationship is not well understood. Penalty points of 0.5 or 1 were assigned to studies that allowed some prior smoking because we view it as adding some degree of uncertainty compared with exclusive use of never-smokers as subjects.
- Verification of smoking status. The ideal is to implement all means available to verify the never-smoking status claimed by subjects. No studies were penalized on this item, but the few studies (i.e., FONT and PERS) that conducted thorough verification were given a bonus of -0.5.

Category B: ETS-Exposure Criteria

- Exposure criteria questionable. The ideal is for a female to be classified as ETS exposed according to a measure of duration (e.g., years of spousal smoking) and a measure of intensity (e.g., number of cigarettes smoked per day by the spouse). Of course, collecting data on measures of exposure is not meaningful unless it enters into the analysis. For the purpose of this report, the objective for case-control studies is to differentiate between subjects as sharply as possible on exposure to ETS using spousal smoking as an indicator. Knowledge is too limited to know how to accomplish this exactly, but extremes wherein the exposed group contains subjects with very little exposure or includes only subjects with very high exposure (while all lesser exposed subjects are classified as "unexposed") should bias results toward the null hypothesis. For cohort studies, GARF(Coh) was penalized because the duration of exposure to spousal ETS was limited.
- Exposure of unmarrieds. Ideally for this report, where the presence or absence of spousal smoking is emphasized as the main determinant of ETS exposure because of its high commonality among studies, subjects would be female never-smokers whose history of exposure to spousal smoke has been reasonably constant over an extended duration (independent of whether a subject may have been married more than once). Studies vary in the extent to which this topic is considered and how it is handled, and assumptions may need to be considered in view of a country's social practices. For example, some studies classify women as unexposed to ETS while unmarried, which may be more reasonable in some cultures than others (e.g., probably more reasonable in Greece than in the United States). Biases resulting from this item are most commonly toward the null hypothesis.

- Verification of exposure status. The ideal is to verify statements regarding present and past exposure to ETS from spousal smoking from other sources. Two studies, AKIB and FONT, were given bonus points for extended efforts in that direction; no studies were penalized.

Category C: Lung Cancer Indication

- Secondary lung cancers possible. The ideal is assurance that all cases are accurately diagnosed with primary lung cancer and that cases are not included where the lung cancer may be secondary to another site. This item is closely related to the next one, which is concerned with the method of diagnosis/confirmation. Bias is toward the null hypothesis.
- Less than 90% confirmation by histology or cytology. The ideal is that the original diagnosis of lung cancer, or a confirmation of it, is conducted by histology. No penalty points are assigned, however, if at least 90% of the cases are diagnosed or confirmed by histology or cytology. Three studies, FONT, KOO, and HOLE(Coh), were given bonus points for extended efforts in diagnostic confirmation. The direction of bias is toward the null hypothesis.

Category D: Interview Type

- Less than 90% face-to-face interview. The ideal interviewing technique is face-to-face by trained interviewers. The effect on the quality of information from other types of data collection is unclear, but telephone interviews and mail-in questionnaires probably increase the rate of misclassification of subject information. The bias is toward the null hypothesis if the proportion of interviews by type is the same for cases and controls, and of indeterminate direction otherwise.
- Unblinded (case-control studies only). The ideal is for the interviewer to be unaware whether the subject is among the cases or controls and the subject to be unaware of the purpose and intended use of the information collected. Blinding of the interviewer is generally not possible in a face-to-face interview. In face-to-face and telephone interviews, potential bias may arise from the investigator's expectations regarding the relationship between ETS exposure and lung cancer incidence. The potential for bias is probably less with mail-in interviews.

Category E: Proxy Respondents

- More than 10% proxy respondents (10% of total for cohort studies and 10% of either total cases or total controls for case-control studies). The ideal is for data to be supplied by the subject because the subject generally would be expected to be the most reliable source. A subject may be either deceased or too ill to participate, however, making the use of proxy responses unavoidable if those subjects are to be included in the study (some studies appeared to exclude them). The direction and magnitude of bias from use of proxies is unclear, and may be inconsistent across studies.

- Uneven distribution between cancer/noncancer subjects. Ideally, the use of proxies is evenly distributed between cases and controls because this might be expected to minimize any net bias remaining from the use of proxy responses. The use of proxies is often much higher for cases than for controls, as one might expect. The effect of proxy distribution on bias is indeterminate.

Category F: Followup (Cohort Studies Only)

- Changes in smoking or ETS exposure not addressed. The ideal is for any changes in personal smoking status or exposure to spousal ETS to be recorded and taken into account in the analysis. If a subject begins active smoking during the course of the study, it may lead to upward bias (from arguments like those given for the effect of smokers who misreport themselves as never-smokers, as discussed in Section 5.2.2 and Appendix B); if the smoking status of the spouse changes, the likely bias would be toward the null hypothesis.
- More than 10% loss to followup. The ideal, of course, is zero loss to followup. The ideal is not achievable in practice, but it seems reasonable to expect loss to followup not to exceed 10%. The bias from loss to followup is indeterminate. Random loss may have less effect than if subjects who are not followed up have some significant characteristics in common.

Category G: Design Issues

- Unsuitable indoor environment. The ideal indoor air environment contains no significant sources of pollution from nontobacco sources that likely contain one or more of the known or suspected carcinogens identified in tobacco smoke or would otherwise be expected to increase the incidence of lung cancer. The presence of high concentrations of indoor smoke from unvented or inadequately vented indoor combustion of coal for purposes of warmth or cooking is commonplace in some regions of China where studies were conducted. This condition is indicated in some studies and has been confirmed from other sources (see reviews in Section A.4 for GENG, LIU, and WUWI). It is expected that indoor coal smoke increases the level and variability of exposure to many of the same carcinogenic agents that occur in ETS, and therefore detection of an incremental increase in lung cancer incidence from ETS would be highly unlikely in such a setting.
- Smoking-related disease in controls (case-control studies only). The ideal is for controls to be free of any disease related to tobacco smoke. This is an issue in some studies where hospital controls are used. Potential bias is toward the null hypothesis.
- Nonincident cases included (case-control studies only). The ideal is for all cases to be incident (i.e., new cases that develop during an interval of time). A few studies began with prevalent cases and then proceeded with incident cases. The use of prevalent cases may introduce some bias of unknown direction because prevalence is affected by survival rate and lung cancer patients generally do not

survive for an extended period. All studies scored on this item were given one-half point, which is in parentheses in most instances, indicating that information in the source is incomplete. Interview information must be obtained from surviving kin or other proxy subjects as well, but that issue is treated separately in a following item. Potential bias is of uncertain direction.

Category H: Analysis Issues

- Uncontrolled for age. The ideal is to control for age by matching on age in the design and then adjusting for age in the analysis of data. There is no clear formula for deciding which variables should be included in a matched analysis, and/or addressed in the analysis of the data collected. Age, however, is likely correlated with total exposure for those classified as exposed to ETS and is suspected of playing a role in cancer etiology. The potential bias from age might be significant, but its likely direction and magnitude depend in an unknown way on the disparity of age distributions between cases and controls.
- Uncontrolled for other factors of importance. This item applies to studies that report an increased association of lung cancer with factors other than ETS exposure but do not consider further whether these factors may be confounders that should be controlled for in the analysis for ETS. For a variable to be a confounder of ETS, exposure to the variable and to ETS must be correlated (which determines the degree of confounding), and the association of the factor with lung cancer must be causal. The correlation should be readily calculable from the study data. Conclusions about causation may not be warranted, but one could still make the necessary calculations under the assumptions that they are causative and then report what implications causation (if correct) would have for the assessment of ETS. The expected effect from controlling for confounders is to move the estimated relative risk closer to the true value.
- Problem(s) with statistical methods. The ideal is that conclusions are drawn from the application of statistical methods that are appropriate to the problem and accurately interpreted. One penalty point was assigned studies where we took issue with the statistical methodology or results. The direction of bias is indeterminate, in general, as the situations differ between studies.

A.4. INDIVIDUAL STUDY REVIEWS

This section of Appendix A contains a review of each epidemiologic study based on the primary references listed in Table 5-1. Descriptions of the four prospective cohort studies are individualized according to the requirements of each study--for example, HIRA(Coh) has a long history of controversy in the literature, so the main arguments are chronicled and discussed as part of the review. As noted previously, reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study

format designed around principles of good epidemiologic practice and features specific to ETS; and (3) a section of comments related to evaluation and interpretation of the study. The author's abstract is, of course, entirely the author's own words; the study description is intended to portray accurately the reference article vis-a-vis items in the study format, so the author's words are used when possible; the comments section is entirely our own assessment of characteristics relevant to study interpretation and utility in this report.

An abstract only is available for the case-control study by Stockwell et al., (1991), referred to as STOC, which has not appeared in print yet. There is insufficient information on the study to include it in the main body of this report. Similarly, an abstract only is available for the second study of Kabat and Wynder (Kabat, 1990), which is included in an addendum following the review of their first study, KABA. The data for many of the studies reviewed have been extracted from a larger, more comprehensive study that includes active smokers. The subjects and their data used for investigation of an association between ETS exposure and lung cancer incidence are referred to as "ETS subjects" and "ETS data," respectively.

A.4.1. AKIB (Tier 2)

A.4.1.1. *Author's Abstract*

"A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers."

A.4.1.2. *Study Description*

This community-based case-control study was conducted in Hiroshima and Nagasaki, Japan, in 1982. The data collected on passive smoking are part of a larger investigation of lung cancer among atomic bomb survivors, the principal objective of which is to evaluate the interactive roles of cigarette smoking and ionizing radiation. This article reports on married female never-smokers, an unmatched subset of the data from the whole study.

The whole study includes a total of 525 primary lung cancer cases diagnosed between 1971 and 1980. Cases were identified from the Hiroshima and Nagasaki Tumor and Tissue Registries and other records. Controls were selected from among the cohort members without lung cancer, two per case in Hiroshima and three per case in Nagasaki. The controls were individually matched to the cases with respect to year of birth (± 2 years), city of residence (Hiroshima or Nagasaki), sex, biennial medical examinations, and vital status. The majority of cases were deceased; those cases were matched to decedent controls by year of death (± 3 years), in addition to the other criteria. Controls were selected from causes of death other than cancer and chronic respiratory disease. Face-to-face interviews were conducted for 81% (82%) of the eligible cases (controls), but 80% to 85% of the interviews for both cases and controls were actually conducted with the subject's next of kin. The mean age of cases at diagnosis is 72.1

years (range 36-94) for males and 70.2 (range 35-95) for females, which is high for lung cancer in Japan. Fifty-seven percent of the cases were pathologically confirmed; the remaining 43% were diagnosed by radiological or clinical findings.

ETS exposure in adulthood was assessed by spousal smoking status, including the average number of cigarettes smoked per day, age the spouse started smoking, and, for those who stopped smoking, the age at cessation. For childhood exposure, a single question was asked regarding whether the subject's mother or father or both smoked when the subject was living at home as a child; responses were obtained for only two-thirds of the subjects. No specific information on exposure to smoking by other household members' smoking or to smoking in the workplace was obtained. ETS exposure data were checked by comparing smoking status with records from RERF surveys in 1964-68 (self-reported by subjects when they were alive). Cases and controls who had never married were excluded. Of the female cases exposed to spousal smoking, 16% had squamous or small cell carcinoma, whereas no unexposed cases had those cell types. No information was provided on location of the carcinomas.

The number of female cases exposed to ETS is 73 out of 94 (number exposed/total) compared with 188 out of 270 female controls (crude odds ratio [OR] is 1.52 [95% confidence interval [C.I.] = 0.88, 2.63], by our calculations). Application of logistic regression to the whole study that *includes active smokers*, gives an adjusted odds ratio of 1.5 (90% C.I. = 1.0, 2.5), similar to the crude analysis. It is not stated explicitly that matching variables were included in the logistic regression model. Four additional analyses were conducted on the ETS data alone (i.e., without active smokers). The authors stratified exposure by number of cigarettes smoked per day by husband (0, 1-19, 20-29, 30+) and obtained a marginally significant trend ($p = 0.06$). No dose-response gradient was found in the association between the number of years the husband smoked cigarettes and the risk of lung cancer in female never-smokers; the odds ratio *decreases* from lowest to highest exposure level (2.1, 1.5, and 1.3). Stratified analysis according to recency of exposure to husband's smoking (unexposed, exposed but not within the past 10 years, and exposed within the past 10 years) shows a significant upward trend ($p = 0.05$). Further stratification of exposed subjects by occupation found that lung cancer risk tends to increase across occupational categories in the following order: housewife, white collar worker, blue collar worker. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the number involved was small. It is reported that additional analyses of the data indicated that factors for matching in the whole study have little influence, but the details are omitted.

Limited histological information is provided. Among cases exposed to spousal smoking, 16% had squamous or small cell cancer, and 84% had adenocarcinoma or large cell cancer. All of the unexposed cases had adenocarcinoma.

The authors conclude that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratio for lung cancer among nonsmoking women tends to increase with amount smoked by their husbands, a trend seen among housewives, as well as among women who work outside the home. There was little association with parental smoking or from passive smoking that had ceased more than 10 years previously.

A.4.1.3. *Comments*

The larger study from which the ETS data are taken was primarily intended to investigate the interaction of smoking and ionizing radiation in atomic bomb survivors of Nagasaki and Hiroshima. The information on passive smoking has been collected posthumously in a large percentage of the cases, requiring heavy use of proxy responses. The response rate was not high, however, because some next of kin refused to answer questions about deceased relatives and no attempt was made to locate next of kin of some subjects who had died or moved away from Hiroshima or Nagasaki. The dependence on proxy respondents raises questions about the validity of the exposure data for some measures, particularly in childhood, and about detailed information such as the number of cigarettes smoked per day, duration of smoking habit, and years since cessation of smoking. Information on childhood exposure was obtained for only two-thirds of the subjects. The omission of data on subjects where the next of kin had refused response or the subject had moved may be a source of bias. The diagnosis of lung cancer was not pathologically confirmed in more than 40% of the cases. Also, it is not clear that the subjects are representative of the target population. They had been exposed to ionizing radiation to varying degrees, whatever implication that may have; they are among the survivors, which may suggest selective characteristics; and their age distribution is high, ranging from about 35 to 90 years of age with an average of 70 years or more.

Only ever-marrieds are included in the ETS subjects, which is helpful in the analysis. There is some ambiguity in the statistical analyses, however, in reference to Tables 2 through 6 (the main results). The tables contain odds ratios that are reported to be the result of logistic regression with matching. The details regarding matching in the analysis are not given, but it is reported that analysis of the crude data and matched logistic regression give similar values. Regarding the analyses for trend, the outcome seems to be sensitive to the measure of exposure used. The odds ratios are strictly increasing for stratification by number of cigarettes smoked per day, but a different pattern emerges when ETS exposure is measured by the number of years the husband smoked cigarettes.

In general, the conclusions are presented more strongly than the data warrant. The assertions are somewhat tenuous that risks tend to increase with amount smoked by the husband, are highest among those who work outside the home and whose husbands are heavy smokers, and decrease with cessation of smoking. Conversely, whereas little association between ETS exposure in childhood and lung cancer is reported, relevant information was available for only two-thirds of the subjects, and its accuracy is questionable because most of that information was provided by proxies. Overall, the observed data suggest that ETS exposure may be related to risk of lung cancer, but there is some potential for misclassification and other sources of bias. Thus, this study provides some useful information on lung cancer risk in passive smokers, but its interpretation needs to be conservative, taking into account the atypical characteristics of the subjects and other concerns described above.

A.4.2. BROW (Tier 3)

A.4.2.1. *Author's Abstract*

"The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979-82 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (OR = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% C.I. = 0.39, 2.97) for passive smoke exposure of 4 or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% C.I. = 0.97, 5.12). The results suggest the need to develop cell type-specific etiologic hypotheses."

A.4.2.2. Study Description

This study was conducted in Denver, Colorado, to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. Because subjects include active smokers, the data on ETS subjects are part of a larger data set.

Cases and controls were drawn from the Colorado Central Cancer Registry. All subjects were diagnosed with lung adenocarcinoma between 1979 and 1982. Cases are white female Denver residents of at least 6 months' duration. Controls are of similar description to the cases, except that they were diagnosed with colon cancer or bone marrow cancer. Controls were matched on a group basis to produce the same age and gender composition. It is not clear if incident cases were used and whether control sampling was cumulative or density.

The subjects are not matched on smoking status, so the data on ETS subjects alone are unmatched for all variables considered in the larger study. Face-to-face interviews were conducted, blindly, on a total of 149 cases and 169 controls, after attrition in selection and follow-up of 47 cases and 38 controls. The subject was interviewed in 31% of the cases and 61% of the controls; the remaining interviews were conducted with a friend or relative. The mean age of the female cases (controls) was 64.9 (68.2) years; no further details are provided. Clinical verification of lung cancer diagnosis was conducted microscopically.

"Exposed" to ETS is used in two ways, depending on context: (1) the husband smoked (presumably "ever-smoked" is intended, rather than "currently smokes," but that is not explicit); (2) the subject was in the presence of tobacco smoke, from any source, 4 or more hours per day on average. Although there are two operational definitions of exposure, neither includes duration of ETS exposure. Questions were apparently asked regarding exposure in both childhood and adulthood, the latter including sources in the home and in the workplace. No indication was found that the data collected from subjects were checked for internal consistency or against other sources. No mention was

found regarding the number of unmarried women in the study or what assumptions may have been made regarding their exposure to ETS when spousal smoking is the source considered (the first of the definitions given above).

The ETS subjects consist of 4 out of 19 (exposed/total) female cases and 7 out of 47 controls, when ETS exposure means the spouse smoked (Definition 1). For exposure from all sources (Definition 2), the corresponding numbers for cases and controls are 4 out of 19 and 6 out of 47, respectively. The crude odds ratio is 1.52 (95% C.I. = 0.39, 5.96) for Definition 1 of ETS exposure and 1.82 (95% C.I. = 0.45, 7.36) for Definition 2 (data communicated from first author, Brownson). A test for trend using hours per day as the exposure measure is conducted on the whole data set for females *including smokers* (33 of 52 cases are smokers and 19 of 66 controls are smokers; the two exposure categories, 4 to 7 and 8 or more hours per day of exposure to passive smoke, contain a total of only 4 cases and 6 controls who are nonsmokers, but 19 cases and 7 controls who are smokers). The method of Miettinen is applied with stratification on age and smoker status ($p = 0.05$ for trend). The data for never-smokers alone were used in a multiple logistic regression to compare subjects exposed 0 to 3 hours per day with those exposed from all sources 4 or more hours per day (Definition 2 of ETS exposure). Adjustments were made for age, income, and occupation. The reported odds ratio is 1.68 (95% C.I. = 0.39, 2.97). (*Note:* It appears that the upper confidence value may be in error. In view of the outcome for the crude odds ratio, a value about twice what is shown might be anticipated.)

To summarize the statistical tests and authors' conclusions, no significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data for both active smokers and passive smokers were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ($p = 0.05$) after adjustment for age and cigarette smoking. However, after adjustment by logistic regression for age, income, occupation, and cigarette smoking, with the two exposure categories for ETS combined (> 3 and $4+$ hours per day), no significant risk was detected.

A.4.2.3. Comments

The study is very small when reduced to the never-smokers alone. The measure of ETS exposure used (hours/day from all sources) is not very specific to differentiate exposed from unexposed persons, particularly exposure 20 to 30 years ago, which may be more relevant than current exposure. Only 15% of the controls have a husband who smoked; only 13% of ETS subjects are exposed from any source 4 or more hours per day. Thus, the cut-point selected by the researchers for general ETS exposure ($4+$ hours/day) may be too high, resulting in a substantial amount of exposure in the "unexposed" group. For either definition of ETS exposure, however, the percentage exposed is extremely low. Details are lacking also in other areas that may have a bearing (e.g., the treatment of unmarried subjects--whether they were present and, if so, the assumption made regarding ETS exposure).

We experienced some difficulty with the statistical analyses. One of the adjusted procedures is the trend test. Perhaps because the number of ETS subjects is so small, smokers were included in the analysis and then a method was used to attempt to adjust the effects of their presence on the outcome. It would be preferable, in our view, to omit the smokers from the analysis entirely. There are so few ETS subjects in the exposure categories (see above) that it

seems highly unlikely that a test for trend would be significant if based on the ETS subjects alone (we did not have the number of ETS subjects by exposure group, however, so we were unable to conduct the trend test to check the outcome).

When the two exposure categories were combined and only the ETS subjects used, the results were not close to statistically significant (OR is 1.68; 95% C.I. = 0.39, 2.97). We also view that result with caution because using the same data for analysis that were used to determine which variables to adjust for may distort the statistical interpretation. There also may be a typographical error in the upper confidence limit because the value shown is only about half the corresponding value for the crude odds ratio.

The remaining analyses are from the crude odds ratio, 1.52 (95% C.I. = 0.39, 5.99) and 1.82 (95% C.I. = 0.45, 7.36), which suggests a possible association between ETS exposure and lung cancer, although it could easily be ascribed to chance in view of the wide confidence intervals. The study has a very strict requirement for classification as exposed to ETS (4+ hours per day from any source of ETS), which is reflected in only 15% of the controls being designated as exposed (40-60% is more typical). This percentage is only slightly higher than the 12% figure based on simply being married to a smoker. The control subjects thus appear unrepresentative of exposure to the target population, or else the classification of subjects exposed is too rigid. The crude odds ratio may be the preferred statistical measure to represent the outcome of the data, but care should be exercised in using the results from this study in conjunction with those of other studies.

A.4.3. BUFF (Tier 3)

A.4.3.1. *Author's Abstract*

"A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties--Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria--to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950-69 to 1970-75 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents ages 30 to 79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment. The exposures of primary interest in the study of lung cancer are those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures."

A.4.3.2. *Study Description*

This population-based case-control study was conducted in six coastal counties of eastern Texas to evaluate the association of lung cancer with occupational and other environmental exposures. Those of primary interest are

associated with occupation in conjunction with tobacco, alcohol, diet, and residential exposures. The ETS subjects are part of this larger study that includes active smokers.

Cases include males and females ascertained from hospital and State records during 1976-80, except for Harris County, which includes only females from 1977-80. All subjects are white (including Hispanic) county residents of at least 6 months. Cases are incident, without restriction to cell type, and histologically diagnosed to eliminate secondary lung cancers (there is some inconsistency in the article on whether all diagnoses were by histology or whether some were by cytology). Controls were selected from State and Federal records, group matched on age, sex, race or ethnicity, county of residence, and vital status. The candidate sample size is estimated in the report at approximately 1,650, including both sexes, of which just over 700 were lost to attrition in selection or followup for various reasons. Face-to-face interviews were conducted, a large number of which were with next of kin as necessitated by inclusion of decedent cases and controls. For example, for females, the number of subject interviews is only 18% for cases (81/460) and 24% (116/366) for controls. The distribution of ages is similar for cases and controls, based on groupings of 10-year intervals.

"ETS exposed" means having ever lived with a household member who smoked regularly. Exposure sources include the home environment during childhood and adulthood but exclude the workplace. There is no mention of whether data on ETS exposure were cross-checked with other interview questions or other sources. No indication was found regarding unmarried females in the sample and how marital status may affect level of exposure to ETS. Some summary information is provided on the distribution of tumors by cell type, but totals include smokers, so they are not reproduced here. The ETS data for females consist of 33 out of 41 (exposed/total) cases and 164 out of 196 controls; for males, the respective figures are 5 out of 11 and 56 out of 90. For the exposure definition given above, the crude odds ratio reported is 0.78 (95% C.I. = 0.34, 1.81) for females (direct calculation from the data yields a value of 0.81; Buffler apparently added 0.5 to all cells to compensate for inclusion of no subjects in some cells). Little difference was found when female smokers were categorized by number of years lived with a household member who smoked. No adjusted statistical analysis is provided to account for variables used in matching for the study as a whole, nor is there a test for trend. The authors conclude that no effect of passive smoking is indicated for lung cancer. No attempt is made to evaluate whether exposure to ETS in childhood or adulthood is a factor.

A.4.3.3. *Comments*

The potential relationship between ETS exposure and lung cancer risk was not a principal issue in the design of this study. As described in the abstract, and more fully in the study description above, other potential etiologic factors were of more central concern. There are several limitations regarding the study's contribution to the epidemiologic evidence on ETS exposure and lung cancer risk. For example, the interview question on exposure to ETS is not very specific. "Having lived with a household member who smoked regularly" does not distinguish between exposure in childhood and in adulthood, between substantial and only light exposure, or between short-term and long-term exposure. One might expect a high percentage of persons to qualify as "exposed" under such a broad

definition, and that is what the study demonstrates: 84% of the controls are classified as exposed. With such a high percentage, both cases and controls may include a number of subjects who have experienced very light exposure to ETS. Another concern in this study is the use of decedent subjects. The majority of both male (86%) and female (82%) cases in the study (including smokers) were deceased. Consequently, a very high percentage of interviews was by proxy (82% of cases and 76% of controls).

This study was conducted in a region with a significantly higher age-adjusted mortality rate for lung cancer than for the United States in general. For all ages combined, the overall excess lung cancer mortality in the Texas study area is approximately 30% to 40% and is considerably higher for some age groups, according to the article. This was the apparent motivation for the study, with emphasis on important occupational and industrial exposures for residents of the Texas coastal area, including those associated with shipbuilding and repair, chemical and petrochemical manufacturing, petroleum refining, construction, and metal industries. If these nonsmoking factors affect the incidence of lung cancer, then they may be confounding the attempt to detect an effect from passive smoking. Appropriate statistical methods need to be applied to adjust the effect of each risk factor for the others.

Other factors may affect the ETS analysis also. Harris County, which is frequently addressed in the article as distinct from the other five counties, was apparently added to the study later (case ascertainment began 1 year later there and included only females; 10 of the 11 hospitals that did not participate are in Harris County). Consequently, there are some regional differences in the study as well as ethnic and racial differences (white and Hispanic). Although the authors took care to match controls on these and other factors, the matching only applies to the whole study (91% and 97% of male and female cases, respectively, are classified as having smoked regularly), not to the ETS subject group specifically, and there is no adjustment for these factors in the analysis. The unadjusted analysis, the insensitive indicator of ETS exposure, and the large use of decedent cases and proxy responses limit the value of this study for assessing any health effects associated with passive smoking.

A.4.4. BUTL(Coh) (Tier 2)

This study was undertaken to explore the role of active and passive smoking in Seventh-Day Adventists in California. Subjects were participants in a larger prospective cohort study of factors affecting health in Adventists.

In 1974, the Adventist Health Study was initiated with the purpose of investigating the associations of a number of lifestyle and nutritional factors with morbidity and mortality in California Seventh-Day Adventists. Registered Adventist households were identified by contacting the clerks of all 437 California Adventist churches. A basic demographic questionnaire sent to all households received a response rate of 58%. In 1976, all subjects aged 25 or older in 1974 were asked to complete a lifestyle questionnaire that included many demographic, medical, psychological, and dietary variables. More than two-thirds of the targeted subjects responded. From the non-Hispanic whites among these respondents, Butler and his colleagues drew two cohorts. One consisted of 22,120 spouses married and living together at the time of completion of the lifestyle questionnaire in 1976 ("spouse-pairs" cohort) and the other of 6,467 individuals participating in an Adventist Health Smog Study of air pollution and

pulmonary disease (the "ASHMOG" cohort); about two-thirds of the ASHMOG cohort also was included in the spouse-pairs cohort.

Subjects received annual forms for self-reporting of hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality was traced in four ways: linkage with California Death Certificate and National Death Index Systems, church clerk notification of deaths entered in church records, and followup of hospitalization history form responses (or nonresponses). Underlying and contributing causes of death were obtained from death certificates. Death certificates were obtained for all reported fatalities.

For the spouse-pairs cohort, subjects were considered unexposed to ETS if their spouses were either never-smokers *or* ex-smokers baptized into the Adventist church--which proscribes tobacco usage--before marriage. Those whose spouses were ex-smokers with less than 5 years of total smoking also were considered unexposed. All other subjects with ex- and current smoker spouses were classified as exposed.

Incidence rates were calculated using person-years. In the spouse-pairs cohort, age-adjusted lung cancer mortality rates for females married to past or current smokers were higher than those for female spouses of never-smokers, yielding relative risks of 1.94 and 2.47 for past and current smokers, respectively. Comparison of wives with ever- versus never-smoking husbands yielded a relative risk of 2.0. The same age-adjusted relative risk resulted when analyses were restricted to the 9,207 never-smoking females included in the spouse pairs. Virtually identical risk estimates resulted from both Mantel-Haenszel and maximum likelihood analyses. None of the relative risks was statistically significant at the 5% level.

In the ASHMOG cohort, the relative risk of lung cancer adjusted for age and past smoking status among females was 1.16 for women who had lived with a smoker for at least 11 years compared with women who had not lived with a smoker; no difference was observed for women who had lived for less than 11 years with a smoker, although this group was only one-tenth as large as the others. A similar pattern was seen among males who had lived for at least 11 years with a smoker, with an adjusted relative risk of 1.17.

In the spouse-pairs cohort, age-adjusted rates of smoking-related cancers (excluding lung cancer) were only slightly higher among nonsmoking females married to smokers than among nonsmokers (relative risk [RR] = 1.06); the relative risk rose to 1.22 when lung cancers were included.

In the ASHMOG cohort, age-adjusted rates using conditional maximum likelihood analysis for all smoking-related cancers were higher among males who lived with a smoker (RR = 1.45 for 1-10 years; 1.74 for 11+ years) or worked with a smoker (RR = 2.62 for 1-10 years; 1.47 for 11+ years). Among females, in contrast, only one (at RR = 1.03) of the four exposed categories had a higher rate than the nonexposed groups.

All lifestyle questionnaires were administered anonymously, thus reducing the potential for inaccurate responses caused by fear of discovery; respondents to the special supplemental ASHMOG questionnaire were assured of confidentiality but not anonymity.

Although causes of death were obtained from death certificates, review of medical records revealed histological confirmation in 99% of the primary malignancies reported among the spouse-pairs cohort. Thus,

substantial misclassification of lung cancer deaths is unlikely. Subsequent study of patients discharged from 1 of the 11 participating Adventist medical centers over a 6-month period indicated that under 2% of study participants failed to report their hospitalizations; serious underascertainment of cases thus also seems unlikely. Losses to followup by study's end totaled only 1.2% of the original study cohort--a very low rate.

Comparing the results of the 1976 questionnaire with those of a supplemental questionnaire given to ASHMOG subjects in 1987, 4.7% of male smokers now reported themselves as "never-smokers" and 1.4% of never-smokers now reported themselves as nonsmokers. Concordance of female responses was even higher. This concordance of responses does not necessarily imply the degree of *accuracy* of responses, only their reliability.

Comparison of responses to the 1987 questionnaire by females revealed that about 6% of those previously classified as not having a smoking spouse now reported having had one; the converse was also true for 6% of the women. These data indicate a mild nondifferential misclassification of exposure, which would push results toward the null.

Information is available on a large number of variables of possible interest as potential confounders or risk mediators. Unfortunately, the modest number of total lung cancer deaths among females in the spouse-pairs cohort (8) or among both sexes in the ASHMOG cohort (13) discourages attempts to control for other potential confounders in addition to age in the analyses. Separate consideration of the association between variables other than passive smoking and age-adjusted lung cancer mortality among women indicated a high relative risk ($RR > 4$) for spousal blue collar occupation. No other variables produced nearly as strong or consistent an association; in fact, the only other consistent association was a relative risk of 1.3 to 1.6 for nonrural status. Unfortunately, no breakdown of blue collar spousal status by exposure groups was presented.

By virtue of its basic design, the inherent minimization of sources of confounding provided by its study population and the level of information available regarding potential confounders, and other sources of bias, the Butler study has many of the key ingredients to produce convincing results. Unfortunately, this potential goes largely unrealized because of the low number of outcome events occurring during the followup period, which for the most part renders stratification or control for multiple factors simultaneously impractical; even stratification by several age or exposure levels produces unstable results.

Nevertheless, the findings of this study are quite consistent with the hypothesis that ETS exposure of nonsmokers is associated with mildly elevated lung cancer, (active) smoking-related cancer, and ischemic heart disease mortality. Insofar as the study data allow for consideration of potential misclassification and confounding effects, neither misclassification nor confounding can account for the observed association. Because of the limited number of outcome events, several possible confounding factors could not be definitively or adequately addressed in the analyses, and the observed associations were not statistically significant; therefore, the study's findings must be viewed as suggestive but not of themselves convincing.

A.4.5. CHAN (Tier 4)

A.4.5.1. Author's Abstract

(*Note:* This study is described in two sources, both of which were used for the description below. Chan et al. [1979] is the more complete description, but it contains considerable attention to active smoking as a cause of lung cancer. Chan and Fung [1982] is a condensed version that specifically addresses nonsmokers. The abstract given here is for the 1979 article. No abstract is provided in the 1982 source.)

"Bronchial cancer is a disease of high and increasing annual incidence in Hong Kong, especially in women, whose age-specific death rates from this cause are among the highest in the world. A case-control study of the relationship of bronchial cancer with smoking was carried out during 1976-77, taking particular note of the histological type of the tumor. Two hundred and eight male and 189 female patients were interviewed, covering about one-half the total number of cases of bronchial cancer registered as dead from the disease in Hong Kong during the period of the survey. The association with smoking was more evident in males than in females, and in squamous and small cell types, as a group, than in adenocarcinoma. Forty-four percent of the women with bronchial cancer were nonsmokers, their predominant tumor being adenocarcinoma, and in them no association could be detected with place of residence or occupation. There was no strong evidence of an association with the use of kerosene or gas for cooking; 23 did not use kerosene. The cause of the cancer in these nonsmoking women remains unknown."

A.4.5.2. Study Description

(*Note:* This description is primarily based on Chan et al. [1979]. Chan and Fung [1982] are cited when used as a reference.)

This study is the earliest of four from Hong Kong that consider ETS exposure as a potential etiologic factor for lung cancer incidence in nonsmoking women. Here, however, that objective is secondary to evaluation of the relationship of bronchial cancer with active smoking.

In the whole study, target cases are the lung cancer patients, male and female, in five hospitals in Hong Kong during 1976-77 who were willing and able to be interviewed. Controls are patients of the same general age groups from the orthopedic wards of the same hospitals as the cases. No specific diseases are excluded. Cases are incident and control sampling is density. The candidate sample size is 208 (189) male (female) cases and 204 (189) male (female) controls. Attrition from selection or followup is not reported but appears to be high. Subjects were personally interviewed, when possible. About half of the estimated number of lung cancer cases diagnosed in Hong Kong during the study period were actually interviewed. Some patients were too ill to answer questions, and more than expected were treated elsewhere than in the hospitals covered. No interviews with next of kin were obtained for the cases interviewed.

The ETS subjects (never-smokers) alone include 84 (2) female (male) cases and 139 (30) female (male) controls. The age distribution of the female cases (controls) is, by percentage, as follows: age less than 40, 7 (5%); ages 40 to 49, 15 (15%); ages 50 to 59, 23 (30%); ages 60 to 69, 23 (22%); and age 70 or more, 32 (28%). Cases with a histological diagnosis were reviewed and verified by reexamination of the pathological specimens. In the

absence of a histological specimen, cytological diagnosis was accepted. In some cases, on histological grounds, secondary adenocarcinoma was suspected, and a few cases were rejected after detailed examination of the clinical records. Of the cases, 46 (55%) were diagnosed by histology, 23 (27%) by cytology, and 15 (18%) by radiology and clinical means. Diagnoses by cell type were as follows: squamous or small cell, 19 (22%); adenocarcinoma or large cell, 40 (48%); others and unspecified, 25 (30%). Of the unspecified, 15 had no histological or cytological verification.

ETS subjects are never-smokers. Classification of a subject as exposed or unexposed to ETS is based on the response to these questions: (1) If you do not smoke, have you been exposed to cigarette smoke from other people at home or at work? (2) Does your husband/wife smoke? (If "yes," how many cigarettes per day?) (The first question is included in Chan et al. [1979]. The second one is from a personal communication of Linda C. Koo.) No information is reported on the distribution of tumors by central and peripheral location.

The ETS data on females based on question 1, above, consists of 50 out of 84 (unexposed/total) cases and 73 out of 139 controls. The authors state that "this is a rather subjective approach to the problem." No statistical estimates are provided; our calculation of the crude odds ratio is 0.75 (95% C.I. = 0.43, 1.30). No clear conclusion is drawn regarding the potential relationship between ETS exposure and lung cancer occurrence, but the authors imply that no connection was found (which the odds ratio and confidence interval amply support). The authors found no particular occupation as being dangerous. Their findings also do not support air pollution as a factor, and they provide no strong evidence that cooking with various types of fuel is relevant.

A.4.5.3. Comments

Although data on spousal smoking were collected along with an indication of the number of cigarettes smoked per day, they are referred to only in the 1982 article, where the authors note without further elaboration that more nonsmoking cases have nonsmoking spouses. It is reported that answers to the question, "Are you exposed to the tobacco smoke of others at home or at work?" gave no indication that other people's smoking was a risk factor for lung cancer in nonsmokers, with 40.5% of cases and 47.5% of controls answering yes to this question. Why the data for spousal smoking are not given and analyzed is unknown. The question about general ETS exposure combines sources in the household and workplace and refers only to current exposure without a measure of duration, which would likely affect any risk associated with passive smoking.

Although it is reported that cases and controls are similar in age, occupation, and other characteristics, comparability is questionable. The article cites a criticism of the whole study (including smokers) for use of orthopedic patients as controls, on the basis that some patients may be hospitalized with smoking-related diseases (e.g., osteoporosis). It was found that the controls smoke more than a group representative of the population of Hong Kong. This would create a bias toward negative association. Although these comments refer to smoking habits, they suggest the potential for selection bias of controls that may extend to nonsmoking controls as well.

It is noted, also, that there are more cases from Hong Kong Island than would be expected from the population distribution of Hong Kong as a whole, possibly due to more success contacting cases in Hong Kong Island than in Kowloon. The authors caution about reaching any conclusion about the distribution of cases within Hong Kong as a whole. The failure to follow up on patients who were eventually treated at other hospitals or were too ill to be interviewed is itself, of course, a potential source of bias.

Other differences are apparent between cases and controls. Among nonsmokers, a higher percentage of cases than controls (1) are Cantonese (81 vs. 70) or (2) have ever cooked with kerosene (73 vs. 60). It is speculated that the Cantonese diet, high in nitrite or nitrate content, may be a factor in lung cancer incidence (Chan and Fung, 1982). More broadly, these comparisons between cases and controls indicate differences in ethnic composition, lifestyle, and socioeconomic status that are difficult to assess.

In summary, ETS subjects are not matched in the design, and an adjusted statistical analysis is not conducted. Consequently, potential sources of bias are not controlled. There is substantial basis to question the comparability of cases and controls, as described above. Data quality is suspect because confirmation of primary lung cancer was limited and cases were missed because patients were too ill to be interviewed personally or were eventually treated at another hospital. Also, the question posed to subjects for classification as exposed or unexposed to ETS is sufficiently general to invite a subjective response. Overall, methodological shortcomings hamper the interpretation of this study's results.

The finding that spousal smoking appears to be more frequent in controls, mentioned in the 1982 report, is noted to be at variance with the Hirayama study, which may have motivated the authors to conduct this secondary analysis of ETS exposure using their previously collected data. Whatever the motivation, the limitations of the original study, which was not designed to assess passive smoking, limit this study's value for assessing ETS exposure and lung cancer.

A.4.6. CORR (Tier 2)

A.4.6.1. *Author's Abstract*

"Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1,338 lung cancer patients and 1,393 comparison subjects in Louisiana, United States. Nonsmokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation."

A.4.6.2. *Study Description*

This study was conducted in Louisiana to investigate the relationship of smoking habits of parents and spouses to lung cancer occurrence. Results of the study were published in 1983; some clarifying details regarding study methodology were supplied in a 1984 paper addressing only the effects of active smoking. The accrual period is not stated; cases are probably a mixture of prevalence and incidence, and controls are cumulatively sampled. ETS subjects constitute a small portion of the whole study, which includes active smokers.

Cases consist of patients diagnosed with primary lung cancer, exclusive of bronchioalveolar carcinoma, from participating hospitals in several Louisiana parishes (counties), predominantly in the southern part of the state. A total of 302 female and 1,036 male cases and an equal number of controls are included in the whole study. Controls were selected from other patients, excluding those diagnosed with emphysema, chronic bronchitis or obstructive pulmonary diseases, or certain cancers (laryngeal, esophageal, oral cavity, and bladder). They were matched to cases on hospital, age (± 5 years), sex, and race. Information about active and passive smoking was obtained by interview (presumably face-to-face and unblinded), with responses obtained from next of kin in 24% of cases and 11% of controls; no information on refusals is provided. ETS subjects were identified by exclusion of individuals who had ever smoked or had never been married, which eliminated 279 female and 1,026 male cases. Removal of subjects with no spousal smoking data eliminated one additional female and two male cases, leaving 22 female and 8 male cases. Similarly, a total of 1,080 men and women were excluded from controls. No demographic comparisons are given, either for the whole study or for the ETS subjects alone, nor is the number of proxy responses provided for the ETS subjects. Histological confirmation was obtained for 97% of cases in the whole study, including ever-smokers.

"ETS exposed" is used in two ways, depending on the analysis given: (1) the spouse has smoked at least 1 pack-year of cigarettes or (2) the spouse currently smokes. Units of exposure are pack-years and current consumption is in cigarettes per day for (1) and (2), respectively. ETS exposure in childhood means that at least one parent smoked during most of the subject's childhood. Types of tobacco smoking other than cigarettes (e.g., cigars and pipes) are referenced indirectly in regard to interview questions but are not included in the data analysis. Other sources of exposure, either at home or in the workplace, are not considered. Never-married women are excluded from ETS analysis, but no information is given on the number of nonsmoking widows and divorcees and how they were handled with regard to ETS exposure. Adenocarcinoma accounts for 54% of lung cancers in nonsmoking women, compared with 22% in women who actively smoke. No further histological breakdowns are provided.

For the main analysis of spousal smoking, exposure constitutes 1 or more pack-years of spousal cigarette consumption. ETS-exposed subjects include 14 (61) of 22 (133) female cases (controls) and 2 (26) of 8 (180) male cases (controls). These data yield a crude odds ratio of 2.07 (95% C.I. = 0.81, 5.25) for females (confidence interval was calculated by reviewers). Among females, stratification by 0, 1 to 40, and 41 or more pack-years of exposure yields odds ratios of 1.0, 1.18, and 3.52, respectively, with the highest exposure category being statistically significant at $p < 0.05$. No adjusted results are presented. It is, however, reported that analyses based on current daily spousal cigarette consumption produced very similar results to the pack-year analyses. In addition, it is reported that neither exclusion of proxy interview data nor restriction to same-race subjects significantly alters the results. Analysis of

parental smoking during childhood embraces the combined population of smokers and nonsmokers, adjusting for smoking status by logistic regression. Maternal smoking is associated with significantly increased estimated risk of lung cancer (OR = 1.38, $p < 0.05$) but paternal smoking is not (OR = 0.83). No association was noted among nonsmokers alone, but the authors note that small numbers preclude adequate analysis of this group.

A.4.6.3. Comments

The study entails a major multicentric effort to assemble hospital-, age-, race-, and sex-matched lung cancer cases and controls from Louisiana hospitals. Its use of trained local interviewers familiar with the region's culture increases the probability of obtaining accurate interview data for the nearly 3,000 subjects involved. Exclusion of active smokers to assess ETS exposure, however, exacts a toll on the study's power and validity. Because the initial matching of cases and controls did not include smoking status, the ETS subjects are unmatched in the analyses of spousal and parental smoking. This potential problem is not addressed by the authors. The lack of any demographic information on cases and controls leaves the comparability of these groups uncertain.

The potential problem of misdiagnosis of primary lung cancer is minimized by the high rate (97%) of histological case confirmations. Eligibility criteria for controls were intended to exclude smoking-related diseases. Some 15% of the controls had cardiovascular disease, however, which has been associated with both active and passive smoking. The authors also speculate that the inclusion of adenocarcinoma, reportedly less smoking-associated than other lung cancers, may have diluted the significance of their results, but they do not present analyses using their extensive histological data to assess this question.

Restriction of the spousal smoking analysis to ever-married individuals eliminates potential bias due to differences between lifelong single and married individuals. Stratification by gender controls for any sex-related differences. Both race and proxy interviews were reported to have no effect on the spousal smoking results, and the spousal smoking association was still observed after division of women into more than and less than 60 years of age. A small number of nonsmoking ever-married cases (8 males and 22 females for this study) hampers efforts to control statistically for other factors; nonetheless, direct adjustment for age and race is needed.

It is concluded that females married to heavy smokers have an increased risk of lung cancer. A significant increase in risk for nonsmokers was found from maternal but not from paternal smoking in childhood. The results for childhood exposure, however, use statistical methods to adjust for the presence of active smokers. It would be preferable, in our view, to remove the data for active smokers prior to analysis. The potential for bias in all of the analyses, which could be in either direction and may or may not be of consequence, needs to be kept in mind when using this study's results.

A.4.7. FONT (Tier 1)

A.4.7.1. *Author's Abstract*

"The association between exposure to ETS and lung cancer in female lifetime never-smokers was evaluated using data collected during the first 3 years of an ongoing case-control study. This large, multicenter, population-based study was designed to minimize some of the methodological problems that have been of concern in previous studies of ETS and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathologic review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were employed to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to ETS from spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from spouse increased, reaching a relative risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared with each control group and when separate analyses were conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings each were associated with a 40% to 60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from father, mother, or other household members."

A.4.7.2. *Study Description*

This study was initiated in 1985 in five major U.S. metropolitan areas to investigate the association between exposure to ETS and lung cancer in female lifetime never-smokers. The study was designed specifically to address this issue and includes only never-smokers. The results reviewed are from an interim report, with the completed study expected to encompass an additional 2 years of case accrual.

Patients were English-, Spanish-, or Chinese-speaking female residents 20 to 79 years of age who have never used tobacco, have no prior history of malignancy, and have histopathologically confirmed primary lung cancer. The lung cancers were originally diagnosed at participating hospitals in Atlanta, Houston, Los Angeles, New Orleans, and the San Francisco Bay area, between December 1, 1985, and December 31, 1988. Two control groups were assembled, one from colon cancer patients and the other from the general population, with the same general eligibility requirements as cases. The population control group, consisting of women selected from the general population by random digit dialing and by sampling from Health Care Financing Administration files, was frequency-matched on age (< 50, 50-59, 60-69, 70+), with two controls per case. The colon cancer controls were frequency-matched to cases by 10-year age groups and by race. The lung cancer group consists of incident cases, but there is no indication

whether density or cumulative sampling was employed for either control group. Exposure data were collected in face-to-face, apparently unblinded, interviews.

Extensive efforts were made to include only never-smokers. For cases and colon cancer controls, medical records were reviewed for tobacco use and physicians were contacted as necessary. Eligible cases not previously excluded and all population controls were contacted by telephone to screen for prior use of tobacco (no more than 100 cigarettes smoked or use of any tobacco in any form for more than 6 months). Urinary cotinine was bioassayed to eliminate any misreported current smokers.

A total of 514 eligible cases were identified, of which 83 were not interviewed for unspecified reasons and 2 had urinary cotinine levels consistent with active smoking. Independent histopathologic review by a pulmonary pathologist was performed for 84% (359/429) of the lung cancer cases, resulting in nine exclusions. Only the remaining 420 cases are included in the study. Colon cancers were not reviewed. Of 489 (1,105) eligible colon cancer (population) controls, 131 (311) were not interviewed and 7 (14) were excluded for high urinary cotinine. Proxies were interviewed for 143 (34%) of the lung cancer cases and 35 (10%) of the colon cancer controls, whereas no proxies were used for the population controls.

Cases and the two control groups all have similar age distributions, with the majority of subjects between 60 and 79 (73%, 74%, and 74% of the cases, colon, and population groups, respectively). The proportion of whites is similar across all groups (63-69%), but the control groups contain a somewhat higher proportion of blacks and lower proportion of other minorities, and a little higher percentage of high school graduates (76% and 79% vs. 68%). Cases and controls are comparable by metropolitan size of adulthood and childhood residences and also by annual income.

Four sources of adult ETS exposure are assessed: smoking by (1) spouse(s) and (2) other household members while living with the subject, and reported exposure to ETS in (3) occupational and (4) social settings. Three sources of possible exposure in childhood (up to 18 years of age) are considered: smoking by (1) father, (2) mother, or (3) other household member(s) while living in the subject's home for at least 6 months. Subjects are characterized as ever- versus never-exposed with a subanalysis by tobacco type (cigarette, pipe, or cigar). Years of exposure are also tabulated. In addition, cigarettes per day for spouse and for other household sources and pack-years for spouse(s) are calculated. No checks on exposure (aside from the cotinine screening) are reported.

Adenocarcinoma is the dominant type of lung cancer among study subjects, representing 76% (311/409) of all cases included in the study (with the exception of 11 cases with "review pending") and also 78% (281/359) of all independently confirmed primary bronchogenic carcinomas among those cases. Other cell types include 12% (48/409) large cell, 7% (27/409) squamous cell, 3% (14/409) small cell, and 2% (9/409) other cancers. No data on airway proximity are provided.

The final study population (for this interim report) consists of 420 lung cancer cases, 351 colon cancer controls, and 780 population controls. Exposure to spousal smoking from all types of tobacco is reported for 294 cases, 231 colon cancer controls, and 492 population controls, yielding similar odds ratios (adjusted for age, race, area, income, and education) of 1.28 (95% C.I. = 0.93, 1.75) and 1.29 (0.99, 1.69) using the respective control groups.

Elevated but statistically nonsignificant observed risks are also observed when cigarette, cigar, and pipe exposure are assessed separately, with either control group. Restriction of analyses to the 281 independently reviewed adenocarcinomas results in stronger associations, with adjusted odds ratios of 1.44 (95% C.I. = 1.01, 2.05) and 1.47 (1.08, 2.01) for all types of tobacco, and increased odds ratios for each type of tobacco as well.

Odds ratios were also calculated for ETS exposure from cigarette smoking alone, with the two control groups combined (the individual results using each control group are entirely consistent). For all lung cancer types combined, the adjusted odds ratios are 1.21 (0.96, 1.54) for spousal smoking, 1.23 (0.97, 1.56) for other household members, 1.34 (1.03, 1.73) for occupational environments, and 1.58 (1.22, 2.04) for social exposure, the last two of which are significant ($p < 0.05$ and 0.01 , respectively). The corresponding odds ratios for adenocarcinoma cases alone continue to be uniformly higher: 1.38 (95% C.I. = 1.04, 1.82), 1.39 (1.05, 1.82), 1.44 (1.06, 1.97), and 1.60 (1.19, 2.14). The odds ratio tends to increase over years of exposure for all carcinomas combined and for adenocarcinoma alone, although not monotonically (without downturns). The tests for upward trend are all significant or suggestive, with p -values ranging from < 0.001 to 0.07 (these p -values are one-half those reported, which apply to a trend in either direction). Finally, for spousal smoking measured in pack-years, the upward trend is significant for adenocarcinoma alone and for all lung cancers together ($p < 0.005$ and 0.04 , respectively).

The authors interpret their findings as evidence of a causal relationship between ETS exposure in adulthood and lung cancer in never-smoking women. In contrast to adulthood, ETS exposure during childhood shows no association with lung cancer, for either all cell types combined or adenocarcinoma alone. Adjusted odds ratios for childhood exposure tend to be slightly (but not significantly) below unity for all exposure sources.

A.4.7.3. Comments

This study is much larger than any other ETS case-control study. More than 400 never-smoking female lung cancer cases were enrolled in just over 3 years, in contrast to the 25 to 75 cases typical of most studies, and two control groups were formed, totaling more than 1,200 subjects. Additionally, the cases and controls are drawn from five widely dispersed metropolitan centers in the United States, representing a population of approximately 18.5 million people, about 8% of the U.S. population. This characteristic increases the generalizability of the study and diminishes the potential for bias related to locale.

Extensive efforts were made to achieve precision and validity, in evidence throughout the study. Cases and controls are highly comparable. They are frequency-matched on age and, for colon cancer controls, on race as well. The distributions of other demographic variables--annual income, childhood residence, and adult residence--are quite similar between cases and both control groups. The control groups contain a little higher (lower) proportion of blacks (Asians and Hispanics) and a higher percentage of high school graduates. These differences, however, should not have influenced the reported associations because all odds ratios are adjusted for race and education.

The use of incident cases reduces the potential for selection bias, and the implementation of two control groups allowed for assessment of potential bias from comparison with cancer patients or the general population alone. The similarity of results obtained from the two control groups suggests little bias from choice of controls.

The use of a multistep procedure to eliminate inclusion of former or current smokers reduces the potential for smoker misclassification as a source of upward bias. As a further safeguard, urinary cotinine was bioassayed for all consenting persons to exclude those likely to be current smokers. This is the only published study we are aware of to implement this precaution. Attention to histopathology is also very thorough. Inclusion of only histologically diagnosed primary carcinoma reduces the likelihood of diagnostic error, which is further reduced by the use of independent histopathologic review of most cases by a single pulmonary pathologist. The study's histopathologic findings bring out two interesting points. First, comparison of cell type diagnoses between hospital and independent reviewers revealed poor concordance for large (56%) and squamous (67%) cell carcinomas, indicating that cell-type-specific analyses for these cancers may be misleading, particularly if all diagnoses are not made by the same pathologist. The histopathologic review also resulted in a net increase of adenocarcinomas from 244 to 281, 78% of the total, a higher proportion than in most but not all other studies. The statistical results were stronger when limited to cases of adenocarcinoma alone.

Exposure information was obtained in the most reliable way, by face-to-face interviews with each interviewer trained and fluent in the subject's primary language. Information for a substantial proportion of lung cancer cases (34%) was obtained from proxy respondents, but fewer proxies were required for colon cancer controls (10%), and none were used for population controls. The use of proxy respondents raises the possibility of information bias, but their exclusion reportedly did not alter the study's findings. The apparent lack of blinding also raises the possibility of interviewer bias, but it is unlikely that such bias (or recall bias, for that matter) would focus its effect on adenocarcinoma. Also, the same relationships hold whether the colon cancer or population controls are used.

Particular attention is paid to all sources of ETS exposure, which is more informative than addressing only spousal smoking, with four sources in adulthood and three in childhood evaluated both individually and in combination. Additionally, subjects are counted as exposed to the ETS of a spouse or other household smoker only while living with the source, giving a more accurate account of exposure than simply determining whether a spouse or household member ever smoked. Consequently, the measures of ETS exposure are more specific by source, and probably more accurate, than in most studies. This reduces bias toward unity in the odds ratio arising from poor distinction between exposed and unexposed subjects. Still, further accuracy might have been achieved by stipulating that smoking must occur in the subject's household or presence, but this is a minor point.

Most of the standard risk modifiers, such as age, race, geographic area, income, and education, are adjusted for in all analyses and thus can be ruled out as sources of the observed results. Although information on diet, occupational exposures, and "other exposures of interest" were collected, these factors are not addressed in this

interim report. Thorough treatment of the possible impact of these factors presumably will be undertaken after subject accrual is finished and published in the completed study.

To summarize, this study was designed specifically and solely to address the topic of ETS as a potential lung cancer risk to nonsmoking women. Several issues were given special attention, such as the potential misclassification of smoking status, histopathologic specificity, recall bias, and source of ETS exposure. Histopathologic specificity has not been convincingly demonstrated in prior studies, and the meaning of "exposed to ETS" has differed widely between studies, even those addressing spousal smoking only. The remaining issues are largely related to controlling potential sources of bias and confounding to enhance validity. The qualitative rigor and completeness of detail in this study is impressive. In addition, it is quite large, which increases precision of estimates and power to detect an association, if it exists. Use of dietary, occupational, and other exposure data in the analyses, along with an additional 2 years of subject accrual, will make the completed study for which this constitutes an interim report even more valuable. As it stands, however, this study is already the largest and most useful case-control study available. Its high quality and the reasonable consistency of the evidence across sources of ETS exposure strongly support an increase in lung cancer incidence associated with passive smoking.

A.4.8. GAO (Tier 3)

A.4.8.1. *Author's Abstract*

"A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were lifelong nonsmokers. The risks of lung cancer were higher among women reporting tuberculosis and other preexisting lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a threefold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the number of meals cooked by either stir frying, deep frying, or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices."

A.4.8.2. *Study Description*

This study was undertaken in Shanghai, China, during 1984-86 to explore reasons for the high rates of lung cancer among women in Shanghai. Potential etiologic factors associated with the high occurrence of adenocarcinoma among females in a population where few women smoke cigarettes is of particular interest. Several potential risk

factors, in addition to exposure to ETS, are investigated. These are included in the abstract above. Smokers are included in the study as well as nonsmokers.

A special reporting system for lung cancer linked with the area's medical facilities was set up for the study period, integrated with the Shanghai Cancer Registry. Incident cases of lung cancer occurring among 35- to 69-year-old female residents of urban Shanghai from February 1984 to February 1986 were interviewed by trained study personnel. Controls were women selected from residents of the urban Shanghai community by stratified random sampling designed to mimic the age distribution of Registry-reported lung cancer cases during 1980-81. It is not clear whether cumulative or density sampling was employed.

Face-to-face interviews were conducted with 672 cases and 735 controls. No cases refused to be interviewed, but 93 died before interview and were therefore excluded; it is not mentioned whether there were any refusals among potential controls. Nonsmokers composed 436 of the cases and 605 of the controls. In the total subject population, distribution of age, education, and marital status between cases and controls is described as similar, except for a larger proportion of controls (32% vs. 20%) in the oldest age group (65-69 years). The age distribution in the ETS population alone is not described.

ETS exposure is based on living with a smoker. For general exposure in childhood or adulthood, exposed subjects are those who ever lived with a smoker. For spousal smoking alone, however, women are ETS exposed only if they lived with a smoking husband for at least 20 years. General ETS exposure sources include all household members but not coworkers. Verification of exposure data was not mentioned. Based on the reported exposure criteria, widows and divorcees would have been included in the spousal smoking data set, whereas never-married women would have been excluded.

For ETS subjects, 246 (375) cases (controls) from the total of 672 (735) cases (controls) are included in Table II of the article that lists the number of cases and controls by number of years lived with a smoking husband. Presumably, the 190 cases and 230 controls not included in the table are unmarried (or never-married) and do not include women married and living with a nonsmoker; no explanation is provided in the article.

Among nonsmoking women included in Table II, 189 out of 246 cases and 276 out of 375 controls had lived with a smoking husband for at least 20 years. These subjects were divided into exposure categories of 20 to 29, 30 to 39, and 40 or more years for comparison with the "unexposed" (< 20 years spousal smoking) subjects. The authors present no unadjusted analyses, but calculations from their raw data yield an overall odds ratio of 1.2 and stratum-specific odds ratios of 1.2, 1.3, and 1.1 for 20 to 29, 30 to 39, and 40 or more years of exposure, respectively. Age- and education-adjusted odds ratios increase with the number of years exposed: 1.1 (95% C.I. = 0.7, 1.8) for 20 to 29 years, 1.3 (0.8, 2.1) for 30 to 39 years, and 1.7 (1.0, 2.9) for 40 or more years. The authors report an odds ratio of 2.9 (1.0, 8.9) for squamous and oat cell cancer for 40 years of exposure or less but present no other type-specific results.

Information on cell type is available for the 542 (81%) study cases diagnosed by histology or cytology; the rest of the cases were diagnosed by radiological or other means. Diagnostic evidence was reviewed by a team of pathologists and clinicians. For the lung cancer cases histologically typed, adenocarcinoma (61%) greatly

predominates, followed by squamous (22%), small cell (6%), and other (11%) types. No breakdowns of tumor type are provided for the ETS group.

The authors conclude that ETS may account for some, but probably few, of the cancers among nonsmokers, because there was little or no association with ever having lived with a smoker. Among nonsmoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk; occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative is the association with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

A.4.8.3. Comments

The number of ETS subjects for analysis is relatively large. Unfortunately, the study is unmatched, with no demographic breakdown of the cases and controls, either for the whole study or for the ETS subjects alone. Controls were selected to make their age distribution similar to that expected for cases in the whole study, but the similarity may not apply to ETS subjects alone. Consequently, there is little basis for evaluating the comparability of cases and controls. Age and education were adjusted for in the analyses, which has some compensatory value.

The use of direct interview with all subjects without reliance on proxies to gather exposure information should enhance the validity of the exposure comparisons. On the other hand, the possible use of unblinded interviewers could have biased results. In light of the lack of association noted for passive smoke exposure as a child or adult, however, it is unlikely that such a bias produced the observed association between spousal smoking and lung cancer. For evaluation of spousal smoking, the reference group can hardly be classified as "unexposed" to spousal smoking because it includes women who lived with a smoking husband for up to 20 years. The investigators probably selected the cutoff level of exposure for their spousal smoking reference group to balance the numbers in each exposure category, as a practical matter. The reference group contains an undisclosed number of women who may have been exposed to spousal smoking for many years, potentially creating a substantial bias toward the null hypothesis (no association between ETS exposure and lung cancer). Consequently, the odds ratios may be biased downwards. The relative comparison across years of spousal smoking, however, is not affected. An increasing trend in the odds ratio was observed, but no statistical test for trend is cited. In a similar vein, it appears that active smokers *may* have been included in the data analysis of overall ETS exposure. That factor, in combination with the use of ever- versus never-exposed classifications without regard to degree or duration of ETS exposure in the analyses, may have reduced the likelihood of detecting any positive association that may exist.

The study appears to have focused on potential risk factors other than ETS. Unfortunately, the effects of these other factors on the ETS results were not explored, even though many of these appeared to be stronger risk factors than passive smoking. Some factors, such as age and education, *were* adjusted for in all analyses. Control for

education should in turn produce a degree of adjustment for factors related to socioeconomic status (e.g., dwelling size and quality of diet).

Overall, the study presents evidence of a mild duration-dependent association between lung cancer and spousal smoking that skirts statistical significance. Several sources of misclassification bias are possible, but most would tend to bias the odds ratio downward. The study was not, however, specifically designed to evaluate the ETS-lung cancer hypothesis. Information was collected and analyzed on a number of other potential risk factors, but they were not adjusted for in the analysis. Coupled with other limitations, this omission reduces the weight of the study's results with regard to ETS, although they support an increase in lung cancer risk with spousal smoking.

A.4.9. GARF (Case-Control) (Tier 2)

A.4.9.1. *Author's Abstract*

"In a case-control study in four hospitals from 1971 to 1981, 134 cases of lung cancer and 402 cases of colon-rectum cancer (the controls) were identified in nonsmoking women. All cases and controls were confirmed by histologic review of slides, and nonsmoking status and exposures were verified by interview. Odds ratios increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. The odds ratio for women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% C.I. = 1.13, 3.95). A logistic regression analysis showed a significant positive trend of increasing risk with increasing exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic class, and year of diagnosis. Comparison of women classified by number of hours exposed a day to smoke in the last five years and in the last 25 years showed no increase in risk of lung cancer."

A.4.9.2. *Study Description*

This study was undertaken in New Jersey and Ohio to investigate the relationship of involuntary smoking to primary lung cancer. All data were collected specifically for this study, and only nonsmokers were included as subjects. Cases are the lifelong nonsmoking women histologically diagnosed with primary lung cancer during 1971-81 in four participating New Jersey and Ohio hospitals. Controls selected from patients with colorectal cancer were matched 3 to 1 to a case on hospital and age (± 5 years). Subjects were not restricted to incident cases, and controls were apparently cumulatively sampled. Exposure data were obtained by blinded, face-to-face interviews with subjects or their relatives.

A total of 1,175 female lung cancer cases were initially identified from medical records. Exclusion of women found to be current or former smokers or not to have histologically verified primary lung cancer eliminated 1,041 of the identified cases, leaving 134 ETS subjects. Interviews were conducted with patient, spouse, or child in about 75% of the subject population, whereas the rest were conducted with another relative. The age distributions of cases and controls are nearly identical.

ETS exposure includes pipe and cigar use as well as cigarette smoking. Three sources of passive smoking are considered, which will be referred to as follows: "exposure to husband's smoke" means having a husband or other related cohabitant who smokes more than occasionally, either (1) anyplace or (2) at home; "general exposure" applies to the smoke of others at home, work, or otherwise who have smoked more than occasionally during the past (1) 5 years or (2) 25 years; and "childhood exposure" refers to experiencing ETS from any source during childhood. Husband's smoking is quantified as cigarettes per day and years smoked; general exposure is given as average hours per day; and childhood exposure is treated as a dichotomous variable. Only 57 percent of the cases were women living with a husband at the time of diagnosis. No checks on exposure status are described, and no classification of subjects by marital status was implemented. Adenocarcinoma (87) predominates among lung cancer cases, followed by large cell (21), small cell and miscellaneous (15), and squamous cell cancer (11); no data on airway proximity are provided.

Ninety of 134 cases were exposed to husband's (or other relative's) smoking at home, compared with 245 of 402 controls, giving a crude odds ratio of 1.31 (reported 95% C.I. = 0.99, 1.73; C.I. calculated by reviewers is 0.87, 1.98). For husband's smoking of 20 or more cigarettes per day, the highest exposure category, the odds ratio increases to 2.11 (1.13, 3.95). Husband's smoking averaged 11.5 cigarettes per day for the exposed subject. For husband's smoking anyplace, 91 of 134 cases and 254 of 402 controls were exposed, giving a crude odds ratio of 1.23 (0.94, 1.60). At the highest exposure category, 40 or more cigarettes per day, the odds ratio is 1.99 (1.13, 3.50). Cigar and pipe smoking alone yields odds ratios of 1.17 and 1.13 for husband's smoking at home and anyplace, respectively. There are statistically significant trends for both husband's smoking at home and for smoking anyplace when measured by cigarettes per day, but not when evaluated by number of years smoked. The odds ratio for ETS exposure from husband's smoke, both total and at home, is calculated by source of interview respondent for the categories of "self," "husband," "daughter or son," and "other." It is readily apparent that the excess risk is attributable to "daughter or son," with some contribution from "other." *None* of the excess risk is attributable to "self" or "husband."

General smoke exposure also shows an association with lung cancer. Exposure over the past 5 and past 25 years yields odds ratios of 1.28 (0.96, 1.70) and 1.13 (0.60, 2.14), respectively. The odds ratios do not increase with increasing level of exposure, however, and none of the associations is statistically significant. No association was found between childhood smoke exposure and lung cancer (OR = 0.9, 0.74-1.12). When the odds ratio is calculated by source of respondent, "other" and "self" account for the excess risk when smoking for 5 years is the measure; for 25 years of smoking, "other" and "daughter or son" account for the excess risk.

Stratification by cell type reveals that husband's smoking is much more strongly associated with squamous cell (OR = 5.00, both for smoking at home and anyplace) than adenocarcinoma (corresponding ORs = 1.33 and 1.48); no association with other cell types was detected. Stratification by age and socioeconomic status suggests little effect of these variables on the results. The results, however, appear to be sensitive to whether the interview data were obtained from the subject or a surrogate (offspring, relative, etc.), as noted above.

A logistic regression analysis including adjustment for age, hospital, socioeconomic status, and year of diagnosis was undertaken for passive smoking. Cigarettes per day of husband's at-home smoking is significantly associated with lung cancer, with an estimated relative risk of 1.7 at exposure of 20 cigarettes per day compared to none. In contrast, husband's smoking outside the home is *not* significantly associated with lung cancer, although the estimated relative risk is 1.26 for 20 cigarettes per day. General smoke exposure is not significantly associated with lung cancer, for either the past 5 years or 25 years of exposure. Adjustment for type of respondent reportedly had no significant effect on the logistic regression results.

A.4.9.3. Comments

The abundance of nonsmoking cases (134) and controls (402) in this study relative to most ETS studies gives it above-average statistical power. Comparability of cases and controls appears good based on their very similar age distributions, matching on hospital and age, and restriction to nonsmokers, although the lack of further demographic comparisons means that divergence on some other factor(s) cannot be ruled out.

A major difficulty in this study, however, arises from the extensive use of proxy respondents. Only 12% (16 of 134) of the case interviews were with the patient. In the stratified analysis, it was found that the husband's smoking at home is positively associated with lung cancer only when the smoking information is provided by a son or a daughter rather than by the patient or her husband. This leads to several possibilities. Perhaps the son or daughter claimed that the patient's husband smoked when he actually did not, thereby shifting cases from the nonexposed to exposed category and increasing the odds ratio, or the patient or her husband claimed that the husband did not smoke when actually he did, thereby shifting cases from the exposed to nonexposed category and depressing the odds ratio. In general, it is thought more likely that true smokers are misclassified as nonsmokers more often than true nonsmokers are misclassified as smokers (see, for example, Lee, 1986, and Machlin et al., 1989). Also, Machlin indicates that proxies tend to misclassify smokers no more often than smokers themselves do. Thus, it may be that the son or daughter data are better than the self or husband data. Alternatively, the difference among the reporting sources may be due only to chance; the results in JANE on self or proxy reports are quite the opposite of those in this paper, with the proxy reports (in this case including the spouse) leading to lower odds ratios than the self-reports.

Another possible problem with this study is the use of colon and rectal cancer cases as controls on the theory that these diseases are not smoking related. A recent paper, Zahm (1991), notes that associations have been found between smoking and these cancers. If these associations carry over to passive smoking, they might bias the result downward.

In general, the detailed results from the stratified analysis in Table 6 of the paper exhibit considerable variation, probably caused by chance. Hence, the overall results in Table 5 of the article, where all the cases and controls are used, may be the most reliable. They indicate an odds ratio of 1.31 (1.24 after adjustment for smoker misclassification bias in the body of this report) for exposure to all types of husband's smoking at home.

The study's exposure assessment methodology is strengthened by the attempt to maintain blinding by not informing interviewers of the study hypothesis or the subjects' disease status. This is impractical in most studies, but given the use of controls who also have cancer and a high proportion of proxy interviews, effective blinding of interviewers *and* subjects may have been largely achieved here. Detailed data on smoke exposure at home as well as elsewhere, including pipe and cigar smoking, were collected. Pipe and cigar smoking are often not considered in ETS studies, thus constituting a potential source of exposure misclassification, and smoking at home should be a more meaningful index of smoke exposure than total smoking. What the authors termed "husband's smoking" actually includes smoking by related cohabitants as well. Presumably, this was done both to increase subject numbers (by not excluding unmarried women) and to enhance detection of passive smoke exposure. However, it could cause some oversight with regard to classification of ETS exposure (e.g., a widow, living with a nonsmoking sister, whose husband had been a heavy smoker). Less understandable is the failure to include smoking by *unrelated* cohabitants and the inclusion of single women living alone. Diagnostic misclassification is unlikely given the histological verification of all cases *and* controls.

Both husband's at-home and total cohabitant smoking are associated with lung cancer, the association being stronger for at-home smoking. Both exposures show a statistically significant general increase in association with level of smoking, with substantial associations only at high levels. The adjusted association for at-home cohabitant smoking is much stronger (OR = 1.7; $p = 0.03$) than that for smoking outside the home (OR = 1.3; $p = 0.13$), a pattern consistent with home smoke exposure rather than some other smoking-related factor as the basis of the observed results. General ETS exposure, in contrast, was inconsistently related to lung cancer in the unadjusted analyses, with a stronger association for exposure within the last 5 years than within the last 25 (possibly attributable to better recall). No dose-response pattern is evident, however, and no association was found in the adjusted analyses.

The adjusted analyses include age, hospital, socioeconomic status, and year of diagnosis in a logistic regression model, along with the passive smoking variable. This adjustment did not significantly reduce the association between husband's smoking at home and lung cancer observed before the adjustment, but it did eliminate any association with general ETS exposure. Thus, the results for husband's smoking at home are probably not biased due to influences of age, socioeconomic status, hospital, or temporal variables. Dietary factors, heating and cooking practices, and family history of cancer were not considered as modifying risk; thus, an effect by one or more of these factors cannot be ruled out.

The heavy reliance on proxy respondents and their uncertain impact on the analysis leaves some uncertainty in interpretation. On the favorable side of this issue, the authors' attempt to blind subjects and interviewers to the study hypothesis lessens the likelihood of potential bias from proxy response, and no significant effect due to respondent type was found in the adjusted analyses. Some of the exposure categories seem vague, but this would tend to reduce the magnitude of the observed association rather than to give rise to one. In summary, this study is suggestive of a dose-dependent association between smoking in the home and lung cancer, with reservations due to the use of proxies.

A.4.10. GARF(Coh) (Tier 3)

A.4.10.1. *Author's Abstract*

"Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's (ACS) prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer."

A.4.10.2. *Study Description*

This study examines the role of passive smoking in lung cancer among married women in the United States. It uses data collected in a large prospective study initiated by Cuyler Hammond of the ACS in 1959. The ACS's objective was to evaluate the association between potential cancer risk factors and cancer mortality. Although data were collected on the smoking status of women and their spouses at the start of the study, Hammond thought the study data should not be used to estimate lung cancer death rates in relation to amount of passive smoking by female never-smokers. Specifically, Hammond notes that the study was not designed for that purpose, and no special information on the subject was obtained; information was available on the smoking habits of the husbands of many of the married women in the study, but not on the smoking habits of the former husbands of women who were widowed, divorced, separated, or married for a second time. More important is his statement that women in America at that time were not generally barred from public and social gatherings where men were smoking, and working husbands who smoked generally did much if not most of their smoking away from home (Hammond and Selikoff, 1981). Similar reservations are expressed by Garfinkel, who also notes that 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married and that the classification of their exposure to their husbands' smoking may not be pertinent (Garfinkel, 1981, p. 1,065).

A total of 29 ACS divisions encompassing 25 states took part in the study; participating counties were in turn selected by division leaders based on feasibility. Data collection was undertaken by networks of volunteers set up within participating counties. Recruitment of subjects and subsequent followup monitoring were undertaken by volunteers who were instructed to enlist qualifying acquaintances. Subjects were restricted to persons more than 30 years of age whose household contained at least one person over 45 years of age. Illegal immigrants and persons who were illiterate, institutionalized, or itinerant were excluded. Detailed questionnaires were distributed to subjects and all members of their household over 35 years of age. These questionnaires covered factors such as diet, alcohol consumption, and occupational exposures as well as smoking habits, but they did not address passive smoke exposure. Volunteers who recruited subjects were given responsibility for tracing the subject's vital statistics for the next 6 years and contacting living subjects again in 1961, 1963, and 1965 to complete a questionnaire on changes in smoking habits. Alternate researchers were appointed as necessary to replace volunteers who moved or quit. Finally,

death certificates were obtained for subjects reported deceased; where death due to cancer was indicated, verification was sought from the certifying physician. Although followup initially ceased with 1965, in 1972 an additional followup was initiated in 26 of the original 29 ACS divisions and terminated in September 1972.

A.4.10.3. *Comments*

The passive smoking study being described was undertaken by assembling a subcohort of married women who reported that they had never smoked and whose husbands completed a questionnaire including smoking habits. This subcohort totaled 176,739 women out of the 375,000 never-smoking women enlisted by the ACS in 1959. Women were divided into three exposure categories based on their husband's smoking status--nonexposed for never-smokers, and low (high) for current smokers of less (more) than 20. Wives of former cigarette smokers and men who smoked cigars or pipes rather than cigarettes were excluded (Garfinkel, 1984); presumably, these had already been excluded from the reported total (176,739). Mortality rates were computed by 5-year age intervals for unexposed women (i.e., wives of nonsmokers), from which the expected number of deaths for exposed women was estimated under the hypothesis that spousal smoking does not affect lung cancer mortality. The ratio of observed to expected deaths in the exposed group provides an age-standardized mortality ratio. This mortality ratio is 1.27 (95% C.I. = 0.85, 1.89) for spousal smoking of under 20 cigarettes per day (low exposure) and 1.10 (0.77, 1.61) for over 20 cigarettes per day (high exposure).

In a separate analysis, women healthy at the start of followup were divided into groups matched on age (5-year grouping), race, education, urban or rural residence, and occupational exposure of husband to dust, fumes, or vapors. Each of these matched groups was then subdivided into zero, low, and high exposure categories. The proportion of observed deaths in each category was multiplied by the proportion of subjects in the smallest category of the matched group relative to that category. This "adjusted" number of deaths was then summed across all groups with a given exposure and compared with the corresponding value for the unexposed (zero exposure) category to provide a mortality ratio. In addition, we conducted a Mantel-Haenszel analysis of mortality using data supplied by Garfinkel that yielded results similar to the author's analyses. Ages 35 to 39 and 70 to 79 were excluded due to insufficient numbers. After stratifying by age and correcting for time under study, the calculated lung cancer risk was greater in subjects whose husbands smoked, but the predicted risk at low exposure was greater than at high exposure. It is notable, however, that the lower risk at higher exposure is entirely attributable to the 50- to 59-year-old age group; otherwise, predicted mortality would be equivalent at the low and high exposure (see Table C-1 of the report under discussion).

The original ACS cohort study was a massive undertaking. By using it as the basis of his cohort, Garfinkel was able to assemble a very large number (more than 170,000) of never-smoking married women. A cohort of this magnitude attains a number of lung cancer cases ordinarily feasible only by means of a large case-control study, while avoiding the attendant pitfalls of potential recall and interviewer bias associated with case-control studies. There are several important limitations, however, that make the results of this study difficult to interpret. The ACS study was

not designed to yield a representative sample of the general population. The sample of women is older (all at least 35 years of age, two-thirds between 40 and 59 at start of followup), more educated (only 5.6% were limited to a grade school education), and contains a much smaller proportion of ethnic minorities (only 6.8% nonwhite) than the general population (Stellman and Garfinkel, 1986). Although not representative of the population as a whole, the relative homogeneity of the subject population does reduce the potential for complications of interpretation that differences in ethnic or socioeconomic factors or both may pose, and it increases efficiency by not including subjects belonging to age groups unlikely to experience significant mortality during followup. Overall, the study population's unrepresentativeness strengthens rather than undermines the study's conclusions. It would have been useful, however, to confirm that exclusion of greatly underrepresented groups, such as nonwhites and persons with no formal education beyond the eighth grade, had no effect on the results.

Because the data on smoking habits were collected prospectively, no information on exposures prior to 1959 was obtained. Exposure history for the years before 1959 may be as important as for the 12 years of followup, however, if lung cancer has a long latency period, such as 20 years or so. Inclusion of persons whose exposure status may have changed markedly by 1959 could be a biasing influence. Neither were changes in exposure status during the followup period considered, despite the availability of data on smoking habits in 1961, 1963, 1965, and 1972. In fairness to the author, keep in mind that our comments are directed at evaluation of the study for its contribution to the issues of passive smoking and lung cancer, although the ACS study was not designed to assess ETS exposure. The only data collected on ETS exposure are based on the spouse's *current* smoking habits at initiation of the study. If the ACS study had been directed at evaluation of health effects of ETS, these issues would likely have been taken into consideration to sharpen the classification of subjects with respect to ETS exposure. Overall, the likely consequence of these factors is to reduce the sensitivity of the study to detect an association between lung cancer and ETS exposure, but the potential for bias in the direction of a false positive cannot be ruled out. For example, if wives of smokers are more likely to become active smokers during followup than wives of nonsmokers, these changes in smoking status could bias results toward finding a positive association with passive smoking. (Relevant to this particular example, the authors state that "very few" subjects reported a change in their smoking status, but provide no further details. Also, 12 or fewer years is a short exposure to produce lung cancer. It is thus probable that any bias introduced by active smoking would be minor; furthermore, the fact that a stronger association was observed for low than for high levels of spousal smoking argues against a confounder associated with spousal smoking. Nevertheless, potential sources of bias may be present that influence the study outcome in either direction.)

During 1959-65, confirmation of primary lung cancer diagnosis was obtained from physicians for 78% of all cancer cases. Among 203 cases of lung cancer in nonsmoking women diagnosed by death certificate, confirmation attempts on an unspecified number of these cases found 34 misdiagnosed as primary lung cancer, whereas 10 primary lung cancers were discovered among cancers diagnosed as nonlung on death certificates. Thus, it appears that only about 85% of the death certificate diagnoses of primary lung cancer were accurate, while a small percentage of primaries were misdiagnosed as cancers of other sites. No confirmation of diagnoses was undertaken during the

period after 1965 when nearly two-thirds (119 out of 182, according to data supplied to reviewers by Garfinkel) of the lung cancer deaths in the ETS study population were reported. In light of the misdiagnosis rates found for 1959-65, it is likely that a substantial percentage of the study's reported primary lung cancers in cases actually arose in other sites, whereas a substantial percentage of reported cancers of other sites actually arose in the lung. The resultant errors in subject classification probably bias the results toward no association (i.e., a false negative conclusion), *if* a positive association actually exists.

Loss of subjects to followup is another source of potential bias. A subsequent report on the ACS cohort (Garfinkel, 1985) states that, whereas more than 98% of the original cohort was successfully traced through 1965, more than 10% (3 of 29) of the original ACS divisions declined to participate in the 1971-72 followup effort. In the study now under review, Garfinkel reports successful followup of 98.4% through 1965 and 92.8% through 1972, apparently not considering subjects in the division who declined to participate in the extended followup as losses. It thus appears that, whereas more than 98% of the original cohort was successfully followed up through 1965, less than 90% of the cohort was targeted for followup through 1972, and losses for this targeted group approached 7%. Such losses not only reduced the number of observed deaths--and, hence, the study's power--but introduced the possibility that differential loss to followup could have distorted the study's results. A greater proportion of losses among exposed subjects than among unexposed could partially mask a true positive association, whereas greater loss among the unexposed could potentially create a spurious association.

Aside from the issues above, the study controls for risk modifiers. Subjects were all of the same gender and marital status, and age was controlled for in all analyses. Analysis by groups matched on race, education, residence, and occupation, along with age, produced nearly identical results as the analyses standardized by age alone, indicating no confounding due to these and unlikely confounding due to other socioeconomic, occupational, or geographic factors.

In summary, this study predicts a weak positive association between spousal smoking at levels of 1 to 19 cigarettes per day and lung cancer, but only slight association at higher exposure levels; neither association is statistically significant. The lack of apparent dose-response pattern undermines the association, but the confidence intervals of the point estimates for the high- and low-exposure groups overlap so broadly that the existence of a dose-response relationship cannot be ruled out entirely. Meaningful interpretation of the results for the issue of ETS exposure and lung cancer, however, is limited. Because the study's objectives were directed elsewhere, the data collected on ETS exposure are limited to the status of spousal smoking at the start of the study. Past history and future changes in status are not well addressed. There is ample indication that death certificate diagnoses are not a reliable source for the selection and classification of subjects. Although a second 6-year followup period was undertaken to increase the followup period to 12 years, its success was limited by incomplete participation and, perhaps, by organizational difficulties related to long-term reliance on volunteers (who may relocate, change interests, lose contact with the subjects originally enlisted over an extended period, etc.). Even if the followup were entirely successful, however, 12 years of followup without regard to exposure experience is not a particularly long period to evaluate the

lung cancer potential for ETS because the latency period associated with active smoking may be on the order of 20 years. Although the ACS study has been an important contribution to its main study objectives, the limited exposure information and other potential sources of bias for the issue of passive smoking and lung cancer leave its assessment in question.

A.4.11. GENG (Tier 4)

A.4.11.1. *Author's Abstract*

Not included in source.

A.4.11.2. *Study Description*

This study was conducted in Tianjin, where China's highest incidence of female lung cancer occurs, to illustrate the relationship between cigarette smoking and lung cancer in females. The study explores both active and passive smoking, so the analyses for passive smoking apply to a subgroup of the larger subject population. The source of the study's subjects and the time over which they accrued are not specified. Subjects resided in Tianjin for more than 10 years. The source of controls is not given, but they consist of females pair-matched with cases on race, age (± 2 years), marital status, and birthplace. It is unclear from the article whether cases were incident or prevalent and how controls were obtained. A draft summary description of this study (Liang and Geng, undated) from Liang indicates, however, that hospitalized cases (96) were matched with inpatient controls and that general population cases (61) were matched with neighborhood controls.

The source of the study's exposure data is not clearly stated, but the draft from Liang indicates that all identified cases and controls were interviewed. No information on collection or verification of smoking or other data is provided. The authors state that cases and controls do not differ significantly in age, education, occupation, race, marital status, birthplace, or residence, but this refers only to the total study population of 157 cases and 157 controls that includes active smokers; the same similarity may not hold for the 54 cases and 93 controls used in the passive smoking analysis. Tumor types are provided for 85% of the total case population but not specifically for the passive smoking subpopulation; adenocarcinomas (36.9%) predominate, being about twice as common as squamous (22.3%) or small cell (19.7%) tumors. Although nearly 85% of the total cases were diagnosed histologically or cytologically, it does not appear that verification of diagnosis or primary status of tumor was undertaken by the authors, and no information on tumor distribution is supplied.

A nonsmoker (which usually means never-smoker) is ETS exposed if the spouse smokes. Presumably, women not currently married are excluded from the analysis, although they could have been included with some assumption made regarding their exposure status. Information on dose and duration of exposure was collected but not used in the passive smoking analysis, and it is not indicated if cigar or pipe smoke was included. ETS exposure from parents and colleagues is reported to have been evaluated. The parental smoking referred to is apparently in

adulthood, as cohabitants in the home, but that is not made explicit. Exposure during childhood was not specifically addressed.

Among the ETS subjects, 34 of 54 cases and 41 of 93 controls were exposed. This yields a statistically significant crude odds ratio of 2.16 (95% C.I. = 1.03, 4.53) for husband's smoking. No analyses adjusted for age or other factors are reported. On a rather confusing note, an odds ratio of 1.86 is cited twice later, but that value is inconsistent with the odds ratio of 2.16 from the raw data. Whether this is an error or the product of an unspecified adjustment by conditional logistic regression, which the authors employ for other purposes throughout the paper, is unknown. The odds ratio increases with the number of cigarettes smoked per day by the husband and with the duration of the husband's smoking. The odds ratios for smoking rates of 1 to 9, 10 to 19, and 20 or more cigarettes per day are 1.4, 2.0, and 2.8, respectively. For 1 to 19, 20 to 39, and 40 or more years of exposure, the odds ratios are 1.5, 2.2, and 3.3, respectively. No tests for trend are cited, and the relevant data are not given. Consideration of ETS exposure from smoking by father, mother, or "colleagues" reportedly yielded no results that are "quite significant." No further details are provided, and it is not clear whether these results consider past smoking status or apply only to current status.

The authors conclude that active and passive smoking are the most important risk factors for female lung cancer in Tianjin. They attribute 35% to 42% of lung cancer occurring in their nonsmoking female population to passive smoking. Female lung cancer also is found to be associated with other factors, such as occupational exposure, with an odds ratio of 3.1 (95% C.I. = 1.58, 6.02); history of lung disease, with an odds ratio of 2.12 (95% C.I. = 1.23, 3.63); and cooking with coal, where the odds ratio increases with the duration of exposure from 1.5 to 5.5 (see Table 8 of this reference).

A.4.11.3. *Comments*

The quality of this study is difficult to assess given the dearth of details supplied by the authors. Certainly the number of nonsmoking cases and controls included is more substantial than in some other studies, and the reported association between passive smoking and lung cancer is statistically significant. Questions regarding the mechanics of data collection and analysis, however, remain unanswered.

Exposure and other data were obtained from hospitalized subjects at bedside and from others in their homes. Apparently no information was obtained from proxy sources; the number of cases (or controls) who could not be interviewed is unspecified. No blinding was employed, but that may not have been feasible. Despite the reported similarity of the demographic characteristics of the total case and control populations, dissimilarity cannot be ruled out within the subgroup used for ETS analyses. Although the whole study, including active smokers, is matched on several variables, that matching need not apply to the ETS subjects alone.

Lack of validation of diagnostic and exposure information may have led to substantial misclassification, although the fact that 85% of the lung cancer diagnoses were obtained via histology or cytology suggests that diagnostic misclassification would not have been extreme. Lack of consideration of former smoking status is a

potential problem. Inclusion of former smokers among the nonsmokers, in combination with a tendency for former smokers to marry smokers, could produce an upward bias in the odds ratios.

Finally, although the crude odds ratio of 2.16 for passive smoking is statistically significant, it does not take into account even the most basic potential confounder--age. For the larger case-control population (including smokers), occupational exposure (OR = 3.1), history of lung disease (OR = 2.64), and cooking with coal (OR = 1.54-5.56, rising with cumulative exposure) are statistically significant risk factors that the authors claim have joint effects with smoking, yet the ETS analysis is not adjusted for these likely confounders. The anomalous odds ratio of 1.86 given later in the results *may* have been adjusted for age or other factors, but there is no way to tell. Also, the detection of an effect of ETS would be unexpected if the study area suffered from high environmental levels of carcinogenic combustion products of coal, as seen in LIU and WUWI. Although the literature contains no studies of Tianjin, Beijing is nearby. Zhao (1990) reports that mean levels of a urinary indicator of polyaromatic hydrocarbon exposure

(1-HP) in nonsmoking housewives are much lower in Beijing than in Shenyang, one of the WUWI study sites, but Wang (1990) found that indoor air pollution, principally due to coal burning, sometimes masks the effect of *active* cigarette smoking.

In summary, the study's results are consistent with the hypothesis that passive smoking increases the risk of lung cancer, but they are not definitive. More detail regarding the mechanics of the study is needed to assess its general validity. If warranted, a clearer and more complete analysis of the study's data regarding passive smoking, including consideration of the information on dose, duration, and potential confounders already available, would then be useful. For the current evaluation of epidemiologic evidence on ETS exposure and lung cancer, too many questions remain about the design and execution of the study to properly interpret the data and assess the authors' conclusions.

A.4.12. HIRA(Coh) (Tier 2)

(Note: Because of the many publications relating to this study, a different format of presentation is used.)

This cohort study and a later case-control study based on it were undertaken to explore the relationship of passive smoking and other factors with lung cancer in Japanese women. Subjects and data used in this study were, however, drawn from a larger study that was not designed to investigate passive smoking.

An exploratory study of mortality determinants targeting adults at least 40 years of age inhabiting 29 health center districts in Japan was initiated in 1965. In autumn of 1965, more than 90% of the target population was interviewed to ascertain the status of lifestyle factors that might affect health (e.g., cigarette smoking, alcohol consumption, and occupation). Individuals, including husbands and wives, were interviewed separately. Followup of the interviewees was conducted using a combination of an annual census of residents and death certificates to monitor mortality. Mortality, as determined by death certificate, was the outcome variable. Hirayama used this study

population to examine the potential effect of passive smoking on lung cancer mortality. In 1981, he reported the results derived from the first 14 years of followup (through 1979) in the *British Medical Journal*.

A total of 142,857 women were interviewed in 1965, of whom 91,540 were nonsmokers whose husbands also had been interviewed regarding smoking status. Using their husbands' smoking status as a surrogate for exposure to ETS, Hirayama calculated lung cancer mortality rates for comparison of women married to smokers with women married to nonsmokers; rates also were calculated using various strata of spousal smoking intensity (number of cig./day), as well as age and occupation. A total of 346 lung cancer deaths occurred in this cohort during the first 14 years of followup.

After standardization for age and occupation, it was found that women whose husbands smoked daily had a higher annual rate of lung cancer mortality than did women whose husbands were nonsmokers or only "occasional" smokers. The rate increased with the level of smoking (e.g., 8.7/100,000 annually for no or occasional smoking, 14.0 for smoking 1-19 cig./day, and 18.1 for 20+ cig./day). Higher rates and a dose-response pattern were observed in women married to smokers after stratification on either husband's age or agricultural work status. Mortality due to two diseases associated with active smoking, emphysema and asthma, was also higher in wives of smokers and increased with exposure. Conversely, mortality due to two cancers not linked to active smoking, cervical and stomach cancer, was no higher in wives of smokers. Consideration of husbands' drinking habits had no significant impact on mortality for lung cancer or other diseases mentioned above.

Further study results appeared in the October 3, 1981, issue of the *British Medical Journal*. Among other things, results were presented by husband's age in 10-year intervals instead of 20-year intervals and for 10 occupational categories instead of 2. These tabulations revealed a statistically significant overall association between husbands' smoking and lung cancer mortality with a dose-response pattern (1.00 RR for nonsmokers plus former smokers, 1.44 RR for medium smokers, and 1.85 RR for heavy smokers). Also of interest was a breakdown of lung cancer mortality and smoking habits in greater detail for both husband and wife. Notably, nonsmoking *husbands* with smoking wives showed a higher lung cancer mortality rate (RR = 2.94) than did those with nonsmoking wives. Because nonsmoking husbands with smoking wives were rather rare, however, the numbers in this stratum were low (only seven deaths); thus, the observed association was not statistically significant.

In 1984, Hirayama published results of an additional 2 years of followup of his cohort in *Preventive Medicine*. The same basic associations reported after 14 years of followup for spousal smoking and lung cancer remained after 2 additional years of followup. Mortality rates increased with increasing exposure after stratification by age of husband, occupation, geographical area, and time period during study; a trend had been reported after stratification for age of wife at start of study only for ages 40 to 49 and 50 to 59. It also was reported that the elevation of lung cancer mortality in nonsmoking women married to smokers was significantly less among women who consumed green-yellow vegetables daily (e.g., for spousal smoking of 20+ cig./day, the RRs for disease mortality were 1.63 and 2.38). No such pattern was observed for ischemic heart disease. In addition, a statistically significant excess of para nasal sinus cancer in nonsmoking wives of smokers had been observed, which showed an apparent

dose-response relationship across four smoking categories, culminating in an RR of 3.44 for spouses of smokers of more than 20 cigarettes per day. That effect dwarfed those related to social class and dietary factors that were also examined.

In 1988, Hirayama reported the results of a case-control study nested within his cohort in *Environmental Technology Letters*. To explore the relationship of women's age at marriage as well as husbands' smoking status with lung cancer mortality, lung cancer cases occurring among nonsmoking women in the cohort study were contrasted with stomach cancer cases as controls. Including only women under 59 years of age at the start of the cohort, the study divided husbands' smoking into three categories--none, 1 to 19, and 20 or more cigarettes per day. Age at marriage also was trifurcated in 19 or fewer, 20 to 23, and 24 or more years. Apparently as a result of exclusion of women over the age limit or because of missing data, only 115 cases and 423 controls were ultimately compared out of the 200 lung cancers and 854 stomach cancers among the nonsmoking female cohort. Adjusting for woman's age and husband's smoking category resulted in odds ratios for lung cancer of 4.95, 1.76, and 1.41 for the respective age-at-marriage groups; the first two of these odds ratios were statistically significant. An additional comparison found that among lung cancer cases, the mean age at first marriage to a smoking husband was nearly 8 years less than the mean age at start of smoking for active smokers.

A greatly expanded nested study was presented in the following year (Hirayama, 1989). The study was designed to explore the potential effect of dietary habits on the relationship between lung cancer and spousal smoking. A "baseline" sample of 2,000 nonsmoking wives, aged 40 to 69 at the start of the cohort study, with known spousal smoking habits was randomly selected from the available cohort of 90,458 for comparison with the 194 lung cancer cases occurring in equivalent subjects within the cohort. After determining that the age distributions of the case and baseline groups were very similar within smoking categories, the combined population was stratified on daily versus less-than-daily consumption for each of five food types (green-yellow vegetables, fish, meat, milk, and soybean paste soup), and wives with smoking and nonsmoking husbands were contrasted to assess differences in dietary habits. After adjustment for wife's age and husband's occupation, only daily meat consumption was significantly more common among wives of smoking husbands, and this was limited to smokers of 20 or more cigarettes per day. Calculation of odds ratios for dietary habits resulted in a "significant" elevation only in daily fish consumers (OR = 1.365, 90% C.I. = 1.05, 1.77; Table IV). A nearly significant *lowering* of the odds ratio was found in daily meat consumers.

Finally, odds ratios were calculated for lung cancer adjusted by wife's age, husband's occupation, and each of the dietary habit categories in succession. A dose-response pattern was observed between lung cancer and husband's smoking that persisted after adjustment for any of the five dietary factors. Odds ratios for the five dietary habit categories ranged from 1.42 to 1.69 for former smokers and smokers of 1 to 19 cigarettes per day and from 1.66 to 1.91 for smokers of 20 or more cigarettes per day compared with nonsmoking husbands. The observed trend was highly statistically significant, regardless of which factor was adjusted for in the calculation.

A.4.12.1. *Chronology of Controversy*

Publication of Hirayama's initial 14-year followup results in 1981 provoked a sizeable volume of commentary in the scientific literature. Following the release of updated results in 1983-84, the study attracted little controversy until the latter part of the 1980s, when criticisms were directed at the study by a number of authors. This process reached its culmination in response to the EPA's release for external review of the document *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*, which placed considerable emphasis on Hirayama's results. An author-by-author, letter-by-letter consideration of the arguments regarding Hirayama's work would be dauntingly duplicative and tedious. Instead, the most-discussed concerns are highlighted below, followed by an overall assessment of the study as it stands today.

Chronology of Selected Events Relevant to the Hirayama Cohort Study

Jan. 7, 1981	Results of cohort study are published in <i>British Medical Journal</i> (282:183-185).
Oct. 3, 1981	Comments and letters to the editor by Kornegay and Kastenbaum (of the U.S. Tobacco Institute), Mantel, Harris, and DuMouchel, and MacDonald regarding Jan. 7 article appear in <i>British Medical Journal</i> , along with the author's reply.
March 3-5 and July additional 10-15, 1983	Hirayama presents updated results for his study cohort incorporating an additional 2 years of followup (for a total of 16 years) to the International Lung Cancer Update Conference in New Orleans and the 5th World Conference on Smoking and Health in Winnipeg, Canada.
Dec. 17, 1983	Updated results of the cohort study are published in <i>Lancet</i> .
1984	Results presented in conference of July 1983, and in summary form in <i>Lancet</i> later that year, are published in full in <i>Preventive Medicine</i> . In addition, Hirayama now reports a statistically significant increase in brain tumors with husbands' smoking. In a roundtable discussion published in the same journal, Lee proposes that misclassification of active smoking status may have biased Hirayama's results.
1985	Another publication of results for the 16-year followup appears in <i>Tokai Journal of Experimental Clinical Medicine</i> .
1987	Hirayama includes previously published study data in a book chapter (Aoki et al., 1987).
1988	Uberla and Ahlborn publish an article from the <i>Proceedings of the Indoor Ambient Air Quality Conference</i> in London (which is essentially the same as an earlier presentation at the 1987 Tokyo International Conference on Indoor Air Quality) criticizing the Hirayama study on several grounds. Their primary assertion is that correction for the cohort's age distribution removes the apparent effect of spousal smoking.
1988	Hirayama publishes the results of nested case-control study based on cohort study data in <i>Environmental Toxicology Letters</i> . Estimated risk of lung cancer is reported to increase with earlier age of marriage to smoker.
1989	Layard and Viren publish a paper presented at the Conference on the Present and Future of Indoor Air Quality in Belgium. Making their own projections of expected deaths and estimating losses to

followup, they conclude that mortality rates were anomalously low and followup losses unacceptably high in the Hirayama study.

- 1989 Hirayama publishes nested case-control results in *Present and Future of Indoor Air Quality*. Positive association of husband's smoking and lung cancer with dose-response pattern is reported after adjustment for dietary variables.

A.4.12.2. Some Major Critical Works

A basic point raised by MacDonald (1981) and others soon after publication of Hirayama's initial results concerned the selection of the study's sample population. It appeared that the 29 health centers included in the study were selected on grounds of convenience rather than to provide a randomly sampled, representative cross-section of the Japanese population. The resultant sample might thus be unrepresentative of the Japanese population as a whole.

Hirayama replied in 1981 that "the satisfactory representativeness [of the study population] . . . with regard to demographic and social indices was confirmed after the survey." He did not, however, provide supporting data. MacDonald (1981) contended that the six prefectures from which the sample was drawn are relatively industry-heavy. Hirayama (1983a) presented data showing that 40,390 of the cohort's wives were married to agricultural workers, 19,264 to industry workers, and 31,886 to "others," indicating some overrepresentation of *agricultural* areas. He later (1990b) cited quality of incidence data, geographical diversity, and coverage of communities of both urban and rural character as well as different dominant industries as key selection criteria. Women aged 70 or more are clearly underrepresented, composing less than 1% of the study's 40-and-older nonsmoking female population; this aspect of the study will be addressed later.

The key problem arising from an unrepresentative sample is that it may limit generalizability of results derived from that sample to the population as a whole. In lieu of good reasons to think that the association between exposure and disease would be different in the study population and the general population, however, the possibility of an unrepresentative sample assumes less importance. Further, in this case, substantial numbers from each major geographical and occupational element of the general population *were* included in the sample. And, as will be seen in the subsequent discussion, similar patterns of association were observed in a number of demographic subgroups.

Misclassification may occur in any epidemiologic study. Most of the critical commentary has focused on potential misclassification of exposure status. Because the study relies on interview data to establish smoking status, misreporting by interviewees may affect accurate classification of both wives *and* their husbands' smoking habits. It has been argued that women are especially likely to misrepresent their smoking habits because smoking is considered less socially acceptable for women than for men, particularly in Asian societies. Such misclassification would tend to reduce the degree of association between passive smoke exposure and its effect(s) if women in the "exposed" and "unexposed" groups were equally likely to misreport their own smoking. One of the most prominent criticisms leveled at the Hirayama study postulates a differential misclassification of smoking status in women. Peter Lee (Lehnert, 1984) raised the argument that if women married to smokers are more likely to be (or to have been) smokers

than women who are married to nonsmokers, and a given percentage of smoking women claim to be nonsmokers, then purportedly nonsmoking wives of spousal smokers will include a higher proportion of active smokers than wives of spousal nonsmokers. This will cause bias in the direction of a positive association. Arguments over the probable size of this bias have occurred with estimated elevations in risk ranging from a few percent to around 50%, depending on assumptions regarding the extent of misreporting, the risk inherent in active smoking, and the degree of marital concordance between smokers (Lehnert, 1984; Wald et al., 1986; Lee, 1987a, b).

Uberla and Ahlborn (1987) raised a number of points regarding the Hirayama study, including those previously mentioned. Citing the "severe selection bias by age," the authors report that the increase in risk with spousal smoking disappears when this bias is corrected for. The study population in fact contained a very small proportion of women aged 70 or older (only about 1%)--so small that the rates generated by nonsmoking married women aged 70 or older are too unstable to provide meaningful results. But by taking the negative results observed in this tiny, unstable stratum of the cohort and weighting them to "correct" for the underrepresentation of this age group, the overall association is made to disappear. Such a "correction" is meaningless. In addition, Hirayama (1990b) has noted that the authors inappropriately adjusted to the total female population rather than to the population of currently married females, and he characterized the adjustment as "neither of scientific significance nor of creative value."

The authors also essentially take Lee's approach to the differential misclassification problem and claim that a modest differential misclassification "leads to risk ratios of around unity." As seen previously, this argument is plausible but purely speculative--and potential biases toward the null are ignored in this and other "corrections." The authors conclude that "the null hypothesis . . . is consistent with the Hirayama data in the same way as is the alternative." But unless one applies the aforesaid "corrections," the Hirayama data are, in fact, *more* consistent with the hypothesis of association than with the null hypothesis.

Layard and Viren (1989) estimated "projected" mortality rates for a cohort with the age and time distribution found in the Hirayama cohort by applying "standard demographic life table procedures" to year- and age-specific life table data from United Nations and Japanese sources. They concluded that female all-cause and lung cancer reported rates were only 76% and 85%, respectively, of projected values. In a separate analysis, the authors also "calculated the numbers of person-years that would have been observed in the cohort if there had been 100% followup" from the reported numbers of deaths. The assumptions used in this calculation are unstated. The authors then estimated, based on the difference between their person-years for 100% followup and the reported person-years, and an assumption that 8 years of observation were lost on average for each person lost to followup over the 16-year course of the study, that approximately 10% of the cohort was lost to followup. Dismissing other possible causes of their estimated mortality deficits, Layard and Viren conclude that "it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality."

Acceptance of Layard and Viren's conclusions must start with acceptance of the validity of their assumptions and calculations, not all of which are stated explicitly. Beyond that, their rejection of alternative explanations for the difference between projected and reported deaths is not convincing. For example, random sampling variation and

regional variations in death rates are both dismissed because neither could produce an effect as large as that observed, although the authors' figures indicate that in combination they could well account for a sizeable portion of the difference. Likewise, the effect of admitting only (initially) "healthy" people to the cohort is dismissed based on the observation of "still very substantial cohort deficits in the last years of the study" without specification of how substantial such deficits were and ignoring the fact that a pattern in which all-cause mortality is most affected and cancer mortality least, as their calculations showed, is the expected pattern for an effect of selection of healthy individuals. Finally, to produce a spurious association, a bias must operate differently on the exposed (smoking spouse) and unexposed (nonsmoking spouse) groups, and no evidence is provided that supports such a pattern. In fact, Hirayama (1990b) reported an approximately 8% loss to followup for the whole cohort, which did not differ significantly by male smoking status. Lacking a pattern of differential loss, the most likely effect of loss to followup is a reduction in the observed associations due to missing mortality events. The effect of selecting an abnormally healthy cohort would in a strict sense limit generalizability of conclusions but would not in itself produce an exposure-effect association when none actually existed.

A.4.12.3. *Critique and Assessment*

Hirayama's cohort is drawn from a study population assembled to explore the associations between a number of potential health-influencing factors determined via interview and subsequent mortality. Thus, the study was not designed to investigate passive smoking and lung cancer specifically. Most of the weaknesses attributable to Hirayama's study derive from this fact.

The only indicator of ETS available to Hirayama was self-reported smoking status at time of baseline interview. Thus, misclassification of spousal smoking status is possible, and change in status over time, modifiers of exposure to spousal smoking, and other sources of ETS exposure cannot be determined.

As previously seen, an overrepresentation of current and former active smokers claiming to be nonsmokers among wives of tobacco smokers probably biases the association between spousal smoking and lung cancer in reported nonsmokers upward. Even the leading proponent of this argument, however, states that unless this bias is much stronger than it appears to be in U.S. and Western populations, it could not account for the major part of the observed results (Lee, 1990). Lack of information regarding the amount of smoking actually done in the home and in the presence of the spouse, room size and ventilation, and other exposure-modifying factors must lead to imprecision in the estimates of exposure via spousal smoking. This imprecision would make an actual ETS-lung cancer association more difficult to detect. The fact that spousal smoking exposure, even if precisely measured, is an imperfect surrogate for total ETS exposure because workplace and ambient environmental sources are not assessed introduces a similar effect. Both of these problems would thus introduce a bias toward the null, suggesting that the study's results are an underestimate of the real association.

Mortality information was derived from death certificate linkage. It has been contended that lung cancer is routinely overdiagnosed as a cause of death on death certificates, thus undermining the study's credibility. But the

resultant misclassification of cause of death would presumably be nondifferential, and thus bias results toward the null. To cause overestimation of the association, a greater proportion of women in the spousal smoking groups than in the nonsmoking group would have to be falsely diagnosed as having lung cancer. Because the study cohort was made up of *nonsmoking* women, there would be little reason for such a pattern (unless, of course, all such cases came from women who falsely reported their initial smoking status or took up smoking in the course of the study *and* the misclassification/smoking habit concordance hypothesized by Lee were actually strongly at work).

No information is given regarding whether the same interviewers interviewed both husbands and their wives. Thus, interviewers may not have been blind to spousal smoking characteristics of interviewees. This is likely to have been of little importance, however, because the outcome--lung cancer mortality--was measured prospectively, and thus did not occur for some time *after* exposure had been assessed. If information bias was to some extent operant in the interview, the most likely scenario would find women whose husbands smoked being probed more strongly for admission of their own smoking than were women whose husbands did not smoke. This would tend to *reduce* underreporting of active smoking in the "exposed" group relative to the "unexposed" group. The result would be to *lower* the observed association between husbands' smoking and lung cancer mortality.

Hirayama's cohort includes only married, reportedly nonsmoking women who were at least 40 years of age and "healthy" at the start of the study. In addition, almost all of these women were under 70 years of age, and agricultural families composed a larger part of the cohort than of the general population. Thus, the cohort does not present a proportionately accurate cross-section of the Japanese population as a whole. Nevertheless, there is little obvious reason why a relationship between spousal smoking and lung cancer mortality found in this cohort should be dismissed on the grounds that it is not generalizable to the greater Japanese (or other) population.

The possibility that confounding by other risk factors explains an observed association must be considered in any study. For lung cancer, of course, smoking, gender, and age are major risk determinants. Restriction of comparison groups to same-gender nonsmokers avoids possible effects due to gender or smoking (but see misclassification discussion regarding smoking status). Age is only partially restricted in the study design, so its consideration in the analysis is essential. Hirayama chose to control for husband's age in analyzing the cohort study's results. All observed associations persisted after such adjustment. Spousal ages *should* be closely correlated, but direct adjustment using the subject's own age rather than the age of their spouse would clearly be preferable. One such analysis *was* supplied (Hirayama, 1983a), and in it a significant association between spousal smoking and lung cancer mortality persisted. Furthermore, in analyzing the nested case-control studies, adjustment for wife's age was used throughout, which produced findings that confirmed the results of the cohort study.

The potential role of confounding by other factors in the observed results has received considerable emphasis. A correlation between smoking and lower socioeconomic status with concomitant lifestyle and environmental differences could be expected. Among these differences, particular attention has been paid to the possible effect of dietary factors (particularly low beta- carotene intake) and occupational exposures, both of which, some hold, should correlate with spousal smoking and thus could bring about the observed association even if spousal

smoking and ETS exposure have no effect. Yet, neither stratification on daily green-yellow vegetable consumption--the best available surrogate for beta carotene intake in the data--nor on agricultural versus nonagricultural occupation of husband eliminated the association between spousal smoking and lung cancer mortality in the cohort study. Similarly, adjustment for husband's occupation and any of five dietary habit characteristics, along with wife's age, yielded similar results in the case-control approach. Thus, neither of the major proposed confounders satisfactorily accounts for the observed results.

Because the data set does not contain the necessary information to examine effects due to differences in cooking practices (such as stir-frying), this cannot be ruled out, although such practices might be expected to co-vary with some of the dietary factors considered in the analyses. Similarly, use of coal for cooking or heating cannot be directly assessed, although a degree of covariance with dietary habits or occupation is likely.

Husbands' drinking habits were only marginally associated with lung cancer risk; mortality rates stratified by both drinking and smoking would have been more useful (and stratification by wives' own drinking habits would have been more useful still).

When lung cancer mortality among wives is stratified by wife's age (in 10-year increments) and husband's smoking category, a clear dose-response pattern is seen only in the 40 to 49 and 50 to 59 age strata, whereas a decrease in mortality with spousal smoking is seen in the 70 and older stratum. Given that the latter stratum includes less than 1% of the cohort and very few deaths, its rates are too unstable to justify much confidence. The dose-response pattern does become weaker with ascending age strata, however, which has led to conclusions of inconsistency with an ETS-lung cancer connection and presence of confounding. Hirayama has proposed that age-related increases in spousal mortality, smoking cessation, and decreased time spent in husband's proximity during the followup period may account for the observed pattern (Hirayama, 1990a). The proximity effect seems questionable because retirement of older husbands would eliminate time spent away from the house at work, but the other arguments are plausible. Alternatively, older women recently married to smokers may be more likely to die from competing causes of death that increase with age before passive-smoke cancer develops. Remarriage, possibly to a spouse whose smoking habits differ from those of the former spouse, also would increase with age and could lead to misclassification of (former) exposure with a bias toward the null. (It is unfortunate that history of former spouses' smoking habits and recency of marriage apparently were not obtained in the baseline interview because if the information had been collected, the aforementioned problems could have been readily addressed.) Temporal trends in some risk modifiers, such as dietary factors, also could play a role.

Confounding cannot be ruled out entirely in certain instances, but the underlying question that must be raised in this regard is the following: *If* the spousal smoking group contains a disproportionate number of individuals with risk-elevating factors such as poor diet, lack of exercise, low socioeconomic status, and occupational hazard exposure, and these factors are sufficient to produce an increase in lung cancer mortality relative to the spousal nonsmoking group, despite an absence of any real smoking effect, *why* does this multitude of risk factors result in elevations of

established smoking-related diseases only and no substantial elevation of risk of other causes of mortality (except brain cancer, which encompasses relatively few deaths)?

In considering the study's results in broader terms, Hirayama's findings are consistent with the hypothesis that exposure of nonsmoking women to passive smoke via spousal smoking increases risk of lung cancer. The observed association is statistically significant. In addition, the persistence of the association after stratification on numerous variables, the observation of a parallel association in nonsmoking husbands of smoking wives, the appearance of associations with other smoking-related diseases, the existence of a dose-response pattern in most analyses of strata containing adequate numbers, and the production of similar conclusions by either cohort or case-control approaches argues against attribution of results purely to chance or confounding.

Possible inclusion of active smokers among "nonsmoking" spouses of smokers through misclassification bias or differential change in smoking status during followup remains the study's greatest weakness. This problem could have been addressed by followup interviews or questionnaires coupled with verification of smoking status by alternative means in a subsample of the cohort, and still could be. In addition, losses to followup and failure to use more sophisticated survival analysis techniques are weaknesses that probably reduced the study's power.

Overall, the Hirayama study provides supportive, although not definitive, evidence that ETS exposure increases lung cancer risk.

A.4.13. HOLE(Coh) (Tier 1)

This prospective cohort study was undertaken in the towns of Paisley and Renfrew, Scotland. The primary objective was to explore the relationship between passive smoking and cardiorespiratory symptoms and mortality, including lung cancer. The towns were selected because they are situated in an area with a high incidence of lung cancer. All persons residing in these towns between 45 and 64 years of age, inclusive, were visited between 1972 and 1976. Each person was asked to complete a self-administered questionnaire and to visit a cardiorespiratory screening center where further interviews were conducted; 80% (15,399 persons) responded.

Participating households in which at least two "apparently healthy" subjects lived were included in the study, yielding a study population of 3,960 males and 4,037 females. Data on smoking habits were obtained from the questionnaire and verified by interview at the screening visit. Mortality among subjects was traced using the Scottish National Health Service Central Register and General Register offices (for death certificate linkage), as well as the national cancer registry system. Results for followup through 1982 were published in 1984 (Gillis et al., 1984). The primary results reported here are for followup through 1985, published in 1989 (Hole et al., 1989). In addition, the results of unpublished data extending followup through December of 1988 are reported (personal communication from Hole to A.J. Wells).

Smoking habits were divided into three categories: persons who have never smoked, former smokers, and current smokers. In addition, the number of cigarettes smoked per day was obtained for current smokers. Both pipe and cigar smokers were excluded from the group who had never smoked. Never-smokers with former or current

smokers as cohabitants in their household were classified as passive smokers; otherwise never-smokers were classified as "controls." This classification yielded 1,538 passive smokers and 917 controls for both sexes combined. The corresponding numbers for females alone are 1,295 and 489.

The number of lung cancer deaths among females occurring in the cohort during the followup period is only six, too small to yield much statistical precision. The unpublished data extending followup through 1988 includes one additional female lung cancer death that occurred subsequent to 1985. The crude relative risk is 2.27 (95% C.I. = 0.40, 12.7), which is in the direction of a positive association between ETS exposure and lung cancer. The extremely wide confidence interval is the result of the small number of cancer deaths being compared and indicates that the data could easily arise when the true value of the relative risk is much larger or smaller than the estimated value. After adjustment for age and social class, the relative risk is 1.99 (95% C.I. = 0.24, 16.72). Lung cancer incidence was somewhat higher than mortality (10 cases vs. 7 deaths), yielding an adjusted relative risk of 1.39 (95% C.I. = 0.29, 6.61). The relative risks for adjusted mortality (5.30) and incidence (3.54) were higher in males than in females but were based on even fewer cases (four deaths, six incident cases).

Although the observed association could easily occur by chance, it is a useful contribution to the pool of evidence on lung cancer and passive smoking. Consequently, it is worth noting that the observed associations are not likely to be attributable to other factors, because they persisted after control not only for age and gender, but for social class, diastolic blood pressure, serum cholesterol, and body mass index. Thus, differences in lifestyle or environmental factors such as diet, housing, and employment between passive-smoking households and nonsmoking households is an unlikely source of the results. Specific adjustment for potential occupational exposures or radon were not carried out, but these variables would presumably co-vary with social class to a great extent.

As for other sources of bias, interviewer bias can be discounted because subjects were "apparently healthy" at interview and supplied smoking information before cardiovascular screening, and the investigators did not begin determining the passive smoking status of subjects until 1983 (for the first published study on this cohort). The extent of loss to followup is not specified, so one cannot tell whether this was a potential source of problems. However, linkage was carried out through two registries for general mortality and an additional registry specifically designed for cancers. Diagnoses of cancer mortality from death certificates were checked against cancer registry records for verification, thus reducing potential inaccuracies attendant on use of death certificates.

Some data regarding misclassification were collected in an additional questionnaire administered to a portion of the cohort at some unspecified point in the study. Among controls, 5% said that their household contained a smoker--presumably someone who had not met the inclusion criteria (e.g., age 45 to 64) for the study. Thus, a small portion of the control group was actually currently exposed, which would produce a slight bias toward the null. Differential misclassification of smokers as never-smokers resulting from concordance of smoking habits among cohabitants cannot be assessed or ruled out, despite the authors' suggestion that persons cohabitating with smokers may be more likely to falsely claim to be smokers themselves, providing a bias toward the null.

In summary, this study appears well designed and executed, but the number of ETS- exposed subjects is small. Although the study carries little statistical weight, there are no apparent methodological problems that would limit its usefulness otherwise.

A.4.14. HUMB (Tier 2)

A.4.14.1. *Author's Abstract*

"As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco-smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse cigarette smoking was found among current or former smokers, never smokers married to smokers had about a twofold increased risk of lung cancer. Lung cancer risk in never-smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never-smokers living with a spouse who smokes cigarettes."

A.4.14.2. *Study Description*

This population-based case-control study was conducted through the New Mexico Tumor Registry during 1980-84. The original purpose was to explain differing lung cancer occurrence in Hispanic and non-Hispanic whites in New Mexico. The study questionnaire included questions on spousal smoking and on indirect exposure to asbestos through a spouse's job. The current report describes the risks associated with those exposures in smokers and nonsmokers. The data on ETS exposure in nonsmokers is extracted from the larger study containing smokers.

For the whole study, a total of 724 eligible primary lung cancer patients were identified, of which 641 were interviewed (89%). About one-half (48%) of the case interviews were conducted with the subject. Information on the remaining subjects was obtained from surrogates, generally the surviving spouse or a child. Cases were collected in two series, the first consisting of patients with cancer incident in 1980-82. That group includes all cases less than 50 years of age and all Hispanics, but not those exclusively. The number of cases was supplemented by a second series of patients with cancer incident to a 1-year period beginning November 1983. Most of the controls were selected by random telephone sampling, but some older subjects were randomly selected from Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category, at a ratio of approximately 1.2 controls per case. Interviews were held for 784 of the 944 eligible controls, with 98% of the responses from subjects.

The term "never-smoker" means not a cigarette smoker, where the latter is defined to be someone who has smoked for at least 6 months. The smoker classification is divided further into current smokers and ex-smokers. The current smoker status includes smokers who have stopped within 18 months before the interview; the ex-smoker status applies if smoking ceased more than 18 months before the interview. Assuming that the minimum 6-month

duration of smoking is intended to apply to current and ex-smokers, never-smokers could have smoked previously for up to 6 months.

An ETS-exposed subject is one ever-married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. No information was obtained on exposure to ETS from other sources, such as from other household smokers, in the workplace, or from parental smoking during childhood. Measures of ETS exposure from spousal smoking include duration of exposure (in years) and the average number of cigarettes smoked per day by the spouse. The ETS subjects (never-smokers) include 20 (4) female (male) cases and 162 (130) controls (the article reports 8 male cases, the number used in much of the analyses, but 4 of those 8 were found to be smokers, personal communication from Humble). The age distribution for the female cases (controls) is as follows: age less than 65, 5 (74); age 65 or more, 15 (88).

The odds ratio for the crude data on female never-smokers is 1.8 (90% C.I. = 0.6, 5.4) for spousal smoking of cigarettes only and 2.3 (90% C.I. = 0.9, 6.6) when spousal smoking also includes use of pipes and cigars. Based on mean cigarettes per day smoked by the spouse, the odds ratio of 1.2 at more than 20 cigarettes per day is somewhat lower than the odds ratio of 1.8 at the lower rate, fewer than 20 cigarettes per day. For duration of exposure, the odds ratio increases from 1.6 at less than 27 years to 2.1 at 27 or more years. It is reported that adjustment for age and ethnicity did not alter these results from the crude analysis. A trend test is included for duration of spousal smoking, but the sample sizes are too small to be meaningful. Application of logistic regression to adjust for variables gives values very close to the odds ratios for the crude analyses shown above for spousal smoking, for use of cigarettes only and also for combined use of cigarettes, cigars, and pipes.

The distribution of cases by cell type is given, but only with males and females combined. The ratios of ETS-exposed cases to the total, by cell type, are as follows: squamous cell (2/4), small cell (1/1), adenocarcinoma (either 6/12, 7/12, or 8/12), and others (either 3/3, 2/3, or 1/3, depending on correct ratio for adenocarcinoma).

The authors conclude that the results indicate increased risk from ETS exposure in never-smokers but not in active smokers.

A.4.14.3. *Comments*

This study evaluates smokers as well as nonsmokers for increased risk of lung cancer from spousal smoking. Not surprisingly, the number of smokers among the cases far outweighs the number of nonsmokers. No evidence of added risk to smokers from passive smoking is found. Such an evaluation, however, puts a great deal of faith in the exposure data and the power of statistical methods to detect what may be only a marginal increase in risk from ETS on top of active smoking.

Of more central concern to this review is the assessment of lung cancer from ETS exposure in never-smokers. The ETS data are taken from a larger study, so the matching no longer applies, although the adjustment for those variables (ethnicity and age category) in the analysis is worthwhile. The article suggests that the high rate of proxy response for cases in the original study (52%) may be due, at least in part, to inclusion of decedent cases. That

topic is not explicitly addressed, however, and controls were not matched to cases on vital status. Never-smokers apparently may have a history of smoking, provided it is of less than 6 months' duration. Whether any never-smokers actually have a short smoking history is not discussed, but the never-smoker classification is less strict than in most studies.

The data are evaluated in a number of different ways, consistently yielding an increased odds ratio. The number of cases, however, is too small (15 exposed, 5 unexposed) for the observed odds ratio to achieve statistical significance. Similar values of the odds ratios might be observed in a larger study, but, of course, that cannot be assumed. The study outcome is consistent with an association between ETS exposure and lung cancer occurrence.

A.4.15. INOU (Tier 4)

A.4.15.1. *Author's Abstract*

(*Note:* No abstract was provided; the following was paraphrased from author's discussion.)

A case-control study on smoking and lung cancer in women was conducted in Kamakura and Miura, both in Kanagawa prefecture, Japan. The two cities are distinctly different in social environment; the former is a residential community and the latter is a fishing village. After stratification on city and age groups, the odds ratio of lung cancer in nonsmoking wives was shown to be 1.58 when husbands smoked fewer than 19 cigarettes a day and 3.09 when husbands smoked 20 or more cigarettes a day. For comparison, the odds ratio for active smoking is 5.50. Although the study size is quite small, it provides additional evidence favoring the passive smoking and lung cancer hypothesis.

A.4.15.2. *Study Description*

This study was conducted to assess the roles of active and passive smoking in the etiology of lung cancer in women. It is unclear how subjects or diagnoses were obtained, but cases are women who died of lung cancer in Kamakura or Miura in the time periods 1980-83 and 1973-81, respectively. Controls, consisting of women who died of cerebrovascular disease during the same timeframes, are individually matched to cases on year of birth, year of death (± 2.5 years), and district of residence. It is not clear whether incident cases were used.

Face-to-face interviews were conducted by public health nurses and midwives. ETS subjects consist of the 28 nonsmoking cases and 62 nonsmoking controls remaining after elimination of 9 cases and 12 controls who were smokers. Husband's smoking status was not available for unspecified reasons in a total of 8 cases and 20 controls, but these figures include smokers as well as nonsmokers. The exact number of nonsmokers for which spousal smoking status was available is not specified but can be back-calculated from what is given (see below). No information is given on the number of proxy respondents, the age distribution of the subjects, or attempts to confirm diagnoses of primary lung cancer.

The term "nonsmoker" is not defined, so it is not clear whether it refers to persons who never smoked or who do not smoke at present. Nonsmoking women whose husbands smoke at least five cigarettes per day are classified as exposed to passive smoking. Considerations of former smoking or marital status, ETS exposure at the workplace or

in childhood, and duration of exposure are not addressed. No attempts to verify the reliability or validity of the data are mentioned.

The number of subjects is not delineated by case versus control and exposed versus unexposed figures. They can be determined from the odds ratio and confidence interval, however, as 18 of 22 (exposed over total) cases and 30 of 47 controls. For nonsmoking women with smoking husbands, the crude odds ratio calculated by the reviewers is 2.55 (95% C.I. = 0.74, 8.78). (*Note:* OR = 2.25 is erroneously reported in the article. The OR value of 2.55 has been confirmed by Hirayama.) When husbands' smoking is divided into two strata (< 19 cig./day and 20+ cig./day), the odds ratios increase with exposure from 1.16 to 3.35, giving a statistically significant trend ($p < 0.05$). Age-adjusted odds ratios of 1.39 and 3.16 are reported for the two strata; adjustment for both age and district yields corresponding odds ratios of 1.58 and 3.09. (*Note:* The first OR value, 1.58, is incorrectly reported in the article as 2.58. The value 1.58 has been confirmed by Hirayama.) The authors conclude that, although the study size is quite small, the results provide more evidence favoring the hypothesis that passive smoking causes lung cancer.

A.4.15.3. Comments

The number of subjects remaining after active smoking and missing data exclusions is small, guaranteeing poor power and lack of statistical significance in the absence of large odds ratios. The details on study design are limited. The source of cases and controls is not mentioned, for example, and it is unclear whether incident or prevalent cases were used.

Information regarding quality control and related concerns is equally sparse. Interviewers used standardized questionnaires, which would help to promote consistency, but no mention is made of blinding them to subject background or study question, the absence of which could introduce interviewer bias (probably in a positive direction). Because cases and controls are stated to have died during the study period, it is probable that proxy respondents were required, but the extent is unknown. In addition, neither duration of ETS exposure from spousal smoking nor exposure from other sources, such as other cohabitants, was considered. The resultant inaccuracy of exposure assessment probably biases the results toward the null. Lack of information on former smoking status or verification of diagnosis may introduce biases of indeterminate direction. Except insofar as the district acts as a surrogate for factors related to socioeconomic status, no risk modifiers other than age or district of residence were considered. The meaning of "nonsmoker" is not given, so treatment of smoking history is unknown, and it is unclear whether the accurate and meaningful segregation of never-smoking subjects needed for effective analysis was accomplished.

Although a substantial odds ratio was observed for husband's smoking, these results are based on a small sample with too few details provided to assess adequately the study's design and execution and its bearing on the evidence, particularly with regard to potential sources of bias. The statistical uncertainty of the odds ratios given is reflected in the extremely wide confidence intervals shown. The test for trend does not add any additional information. It is basically a restatement of the significant comparison between the heavily exposed group (husband

smokes > 20 cig./day) and the unexposed group. Unfortunately, the brevity of the description of this study in the source available severely limits its utility.

A.4.16. JANE (Tier 2)

A.4.16.1. *Author's Abstract*

"The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case-control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of 'smoker-years,' determined by multiplying the number of years in each residence by the number of smokers in the household."

A.4.16.2. *Study Description*

This study was undertaken in New York State to clarify the role of exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers. Interviews were conducted with former smokers as well as never-smokers initially (Varela, 1987), but because matching was carried out on smoking status, only never-smoking case-control pairs were included in the analyses for this article. The study includes both males and females, which are combined in all of the analyses. There are 146 (45) female (male) pairs.

Cases are never-smokers aged 20 to 80 years newly diagnosed with lung cancer at 125 referral centers in New York from July 1, 1982, to December 31, 1984. Controls are cumulatively sampled never-smokers identified from files of the New York Department of Motor Vehicles. Controls are individually matched to cases on age (± 5 years), gender, and residence. In addition, the same interview type (proxy or direct) was used for controls as for their corresponding cases. Exposure data were collected face-to-face via standardized questionnaire, and interviewers were apparently uninformed of the subject's diagnosis.

From the 439 case-control pairs interviewed, 242 pairs containing former smokers and 6 pairs with a mismatch on the source of response were excluded. Of the remaining 191 pairs used in the ETS study, interviews were conducted directly with the subjects in 129 pairs (68%) and with proxies in 62 pairs (32%) (if a proxy was interviewed for a case, then a proxy was used for the matching control as well). No demographic comparisons were provided for the ETS cases and controls. For the whole study including smokers, the mean age of cases and controls is nearly identical (67.0 and 68.1, respectively; Varela, 1987). Histological verification of diagnosis was obtained for all but five cases (for whom only clinical information was available) out of the initial population of 439.

Persons smoking no more than 100 cigarettes over the course of their lifetime qualified as never-smokers for this study. Cigar or pipe smoking was apparently not considered. Exposure to ETS was deemed to occur when a smoker lived in the subject's household at any time from infancy to adulthood. Both total household smoke exposure and spousal smoke exposure were determined. Preadult (before 21 years of age) and adult exposure were examined separately. Exposures were computed in units of "smoker-years," the total number of years lived with each smoker summed over smokers. In addition, pack-years were calculated for spousal smoking. Workplace exposure also was estimated by smoker-years, whereas exposure in social settings was estimated subjectively on a scale from 1 to 12 for each decade of life and summed. Exposure data were not checked, and marital status was not considered in the analyses. No information on tumor type or location was provided for the never-smoking population.

Preadult exposure to 24 or more smoker-years occurred in 52 (29) cases (controls), whereas 82 (94) were exposed to 1 to 24 smoker-years and 57 (68) were unexposed. Odds ratios were calculated using matched-pairs regression analysis. Preadult passive smoking yielded increasing odds ratio of 1.09 (95% C.I. = 0.68, 1.73) for 1 to 24 smoker-years and 2.07 (1.16, 3.68) for 25 or more smoker-years. The odds ratios for adult exposure are low but also increase--from 0.64 (0.34, 1.21) at 1 to 24 smoker-years to 1.11 (0.56, 2.20) at 75 or more smoker years. The odds ratios for lifetime exposure increase from 0.78 (0.36, 1.67) at 1 to 24 smoker-years to 1.80 (0.83, 3.90) at 25 to 99 smoker-years and then dip to 1.13 (0.56, 2.28) at 100 or more smoker-years. Spousal smoking was not significantly associated with lung cancer. In fact, when results were stratified by type of interview, proxy interviews yielded strong and, in some instances, statistically significant negative associations for spousal smoking, with odds ratios between 0.20 and 0.68 for ETS expressed in terms of present or absent, smoker-years, and pack-years of exposure. The odds ratios for direct interviews, in contrast, range from 0.71 to 1.10 and are uniformly higher than the odds ratios for corresponding proxy responses. Workplace exposure to 150 or more person-years yielded an odds ratio of 0.91 (0.80, 1.04), whereas a social setting exposure score of 20 led to a statistically significant *decreased* odds ratio of 0.59 (0.43, 0.81).

The authors conclude that they found a significant adverse effect of relatively high levels of exposure to ETS during early life (before age 21). For those who were exposed to 25 or more smoker-years in their first two decades of life, the risk of lung cancer doubled. By contrast, the authors found no adverse effect of exposure to ETS during adulthood, including exposure to a spouse who smoked. This lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

A.4.16.3. Comments

The number of never-smoking cases is relatively large, resulting in above-average statistical power for evaluation of ETS effects. Controls were matched to cases on smoking status, as well as the key demographic factors of age, gender, and neighborhood. Comparability of cases and controls was likely good, as evidenced by the similar mean ages for the total population, although no other comparative information is available. In view of the use of

population-based, basically healthy controls, it is questionable that any attempted diagnostic blinding would be effective. The study's matching on smoking status with subsequent retention of matching and use of matched-pairs analysis for ETS exposure effectively eliminates potential effects on risk attributable to age, gender, or residence, and it makes bias by related factors (such as socioeconomic status) less likely. A rare feature is the use of matching on interview type (i.e., proxy or subject direct) to control for bias due to this source. Comparison of spousal smoking results for direct and proxy interviews, however, indicates consistently lower estimated risks from proxies. This suggests that use of proxy respondents did not merely lead to increased random misclassification but might have biased the outcome toward a negative association. The authors posit that proxies of lung cancer patients may be more likely to underreport exposure than those of control subjects. Curiously, however, although the authors report that odds ratios "frequently differed according to type of interview," they do not specify how the odds ratios differed for exposure other than spousal smoking. Also, the composition of the proxy groups--relative proportions of spouses, other relatives, and friends or associates--is never discussed, leaving unexplored the possibility that misreporting by spouses of cases may lie at the heart of the observed discrepancy. It is also interesting that the outcome of self-responses versus proxy responses in this study is in the opposite direction of the findings in GARF. Diagnostic misclassification is unlikely, given the histological verification of nearly all cases.

The restriction of subjects to persons smoking no more than 100 cigarettes in their lifetime theoretically eliminates active smoking as a source of bias, although no verification of smoking status was undertaken. Consideration of potential sources of ETS exposure is commendably thorough, and the calculation of total years of living with smokers, regardless of relation to the smoker, as an index of household smoke exposure minimizes the possibility that any source (e.g., roommates) is overlooked. In contrast, the index of exposure in social settings is highly subjective, and persons more habituated to passive smoke may report a given exposure as less severe than persons less accustomed to smoke, thus creating a negative bias. The proportion of controls classified as exposed to ETS is 80%, which is high in comparison with other studies. This suggests that some exposed controls may have only minor exposure to ETS, making detection of an association (if present) less likely. Unlike almost every other ETS study, males and females are combined in the analysis and only the joint results are reported. Because there are 45 (146) pairs of males (females), the sample sizes are sufficient to warrant reporting odds ratios separately by sex and to test the hypothesis of no difference due to gender.

Lung cancer odds ratios for adulthood, lifetime, and spousal smoking are consistently well below 1 for low ETS exposure relative to nonexposure, as if exposure had a protective effect. Thereafter, however, the odds ratios associated with increasing levels of exposure are suggestive of an upward trend in response. Although we would not dismiss the occurrence of this outcome as attributable to chance alone, it is consistent with the baseline lung cancer mortality rate in the control population simply being higher than that of the case population for reasons other than exposure to spousal smoking. A pervasive (systematic) negative bias linked with exposure could also produce such an effect. Both of these contingencies are necessarily speculative because there is no evidence in the article to support either, aside from the outcome of the data analysis. Further fueling the speculation, however, are the markedly lower

odds ratios obtained from surrogate responses, indicative of some source of bias acting unequally on proxy and nonproxy sources. Also speculative is the idea that using predicted responses from a model that fits the data poorly might produce such an effect, but that level of detail is beyond the scope of most published articles, including this one. Some discussion of these issues by the authors, as well as *separation of the analyses by sex*, would enhance interpretation of results and facilitate their comparison with results of other studies on females.

The authors' finding that exposure during childhood and adolescence appears to influence subsequent lung cancer risk more than exposure during adulthood raises some interesting possibilities. More time may be spent in proximity to a household smoker (particularly the mother), on average, in childhood than in adulthood. According to data presented by K.M. Cummings (Roswell Park Memorial Institute, Buffalo, New York) at the Science Advisory Board meeting on EPA's draft ETS report (U.S. EPA, 1990), on December 4-5, 1990, heavy childhood exposure is a better surrogate for total lifetime exposure than is spousal exposure. Also, early exposure may appear to become a risk, either due to a long latency period for lung cancer or, perhaps, due to increased susceptibility at an earlier age. The results suggesting an effect from early exposure but not from spousal smoking are more nearly atypical than reinforced by other studies, though, and the number of exposure sources considered raises the possibility that the strength of association seen for preadult exposure may be due to chance. However, after elimination of 78 pairs with incomplete marriage or household exposure data, the association persisted and was strengthened ($OR = 2.59$), arguing against chance as the major influence. It is unclear what role, if any, negative bias due to proxy respondents may have had in the nonspousal analyses.

In summary, the findings for preadult exposure are not readily attributable to chance or confounding, although some role of interviewer bias or other factors such as diet cannot be ruled out. No association with lung cancer incidence is observed for spousal smoking. The authors conclude, however, that, spousal smoking aside, other sources of household ETS exposure support the conclusion that exposure to ETS can cause cancer. That conclusion is not unequivocal in our view. In general, the odds ratios (aside from preadulthood exposure) tend to be low but trend upward with exposure, exhibiting more of a patterned response than one might expect to see due to randomness. This is puzzling because there is no apparent source of bias and the study appears to have been conducted with considerable forethought and thoroughness. The only exception noted is the lack of separate analyses and comparisons of males and females. These concerns notwithstanding, the study is a useful addition to the literature on ETS exposure and lung cancer.

A.4.17. KABA (Tier 2)

A.4.17.1. Author's Abstract

"Among 2,668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in 'validated' nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1,919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with

equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption, or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (RR = 3.10, 95% C.I. = 1.11, 8.64), but significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed."

A.4.17.2. Study Description

In 1969, the American Health Foundation began interviewing newly diagnosed lung cancer patients with cancer at sites potentially related to tobacco use for a case-control study (Wynder and Stellman, 1977) that is still ongoing. The current article considers the data on lung cancer in nonsmokers alone collected from newly diagnosed lung cancer patients between 1971 and 1980. Several factors are of interest: histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and ETS exposure. The number of nonsmokers among the cases is small, so the authors consider the results to be preliminary.

The study from which the data on lung cancers in nonsmokers are extracted is a very large effort that includes tobacco-related cancers at multiple organ sites and includes smokers as well as nonsmokers. The cases are from approximately 20 hospitals in 8 U.S. cities (about one-third from New York City). With reference to the lung cancer cases in that study, histologic type of lung cancer was determined from pathology reports and discharge summaries. Secondary lung cancer cases were excluded. Controls consist of hospital patients with diseases unrelated to tobacco use who were pair-matched with cases on hospital, age (within 5 years), sex, race (with five exceptions), date of interview (within 2 years), and nonsmoking status. Cases appear to be incident, and control sampling is density. All subjects were interviewed while they were in the hospital. The questionnaire for the interviews was expanded in 1976. Questions on exposure to ETS were not included, however, until an addendum to the questionnaire in 1978, which was then modified in 1979.

The term "nonsmoker" applies to subjects who have smoked fewer than one cigarette, pipe, or cigar per day for a year. The term "never-smoker" is used interchangeably. Independent of the intended definition, however, subjects whose hospital charts indicated any record of smoking, even in the remote past, were excluded from the nonsmoker classification. ETS subjects include 53 (25) females (males), after combined attrition of 22 (9 without primary lung cancer and 13 with a record of smoking). The age distribution of the female cases (controls) is as follows: age less than 50, 12 (15); age 50 to 59, 26 (24); age 60 to 69, 29 (34); age 70 or more, 30 (24). Histologic data on lung cancer type are given for female cases: squamous cell (16), adenocarcinoma (60), alveolar (12), large cell (4), and unspecified (5). The authors report that exposed cases did not differ from the unexposed cases in the distribution of histologic type.

A person is "ETS exposed" (1) at home, if currently exposed on a regular basis to family members who smoke, (2) at work, if currently exposed on a regular basis to tobacco smoke at work, and (3) to spousal smoke, if the spouse smokes. There are data on 53 cases and their controls for exposure at home and at work, but data on only 24 cases and 25 controls for spousal smoking. This is because of the change in the questionnaire from 1978 to 1979 and because spousal smoking was only applicable for women currently married. Because nonsmoking status was a variable for matching, the 53 pairs of cases and controls for analysis of exposure at home or at work are matched; the data for spousal smoking, however, are technically not matched. There is no indication at all of an association between ETS exposure and lung cancer for women from exposure at home, at work, or from spousal smoking. For ETS exposure at home, there are 16 of 53 (exposed/total) cases and 17 of 53 controls; for exposure at work, the figures are 26 of 53 cases and 31 of 53 controls; and for spousal smoking, the data are 13 of 24 cases and 15 of 25 controls. No statistical calculations are provided for females. From our calculations, the odds ratio for spousal smoking is 0.79 (95% C.I. = 0.25, 2.45). (Among male subjects, exposure to ETS in the workplace was slightly significant, $p = 0.05$, as reported in the article.) For other potential risk factors for lung cancer in women other than passive smoking, it was found that cases were more likely than controls to have worked in a textile-related job (OR = 3.1; 95% C.I. = 1.1, 8.6), but the significance of the finding was not clear. It also was found that more female cases had a history of pneumonia compared with controls, but no interpretation could be attached to the observation.

A.4.17.3. Addendum

Unpublished preliminary results of a study of ETS and lung cancer in never-smokers conducted at the American Health Foundation have been reported at two meetings--The American Public Health Association (APHA) 119th Annual Meeting, Atlanta, Georgia, November 10-14, 1991, and The Toxicology Forum, 1990 Annual Winter Meeting, Washington, D.C., February 19-21, 1990. A completed report for our review was not available at the cutoff date for inclusion in this document (personal communication with the first author, Dr. G.C. Kabat). Enclosed below is the abstract for the APHA meeting.

RISK FACTORS FOR LUNG CANCER IN LIFETIME NONSMOKERS

Geoffrey C. Kabat, Ernst L. Wynder

Risk factors for lung cancer in lifetime nonsmokers (NS) were assessed in a hospital-based case-control study carried out between 1983 and 1990. The study population consisted of 41 male and 69 female NS cases and 117 male and 187 female NS controls matched on age, race, hospital, and date of interview. Evidence of an effect of exposure to ETS was inconsistent. In males, there was no difference between cases and controls in reported exposure to ETS (yes/no) in childhood, in nonsignificant association with exposure in childhood (OR = 1.6, 95% C.I. = 0.9, 2.8), but no association with exposure in adulthood at home or at work. Male cases were somewhat more likely to have a smoking spouse (OR = 1.6, 95% C.I. = 0.7, 3.9),

whereas there was no difference in females. Cases and controls did not differ in reporting a history of previous respiratory diseases. Female cases were more likely to report a history of radiation treatment (OR = 4.3, 95% C.I. = 1.5, 12.3). In females, but not in males, a significant inverse association was observed between body mass index (based on self-reported weight 5 years prior to diagnosis) and lung cancer risk.

A.4.17.4. *Comments*

Although the study contains more than 2,600 patients, only a small number of nonsmokers are available because questions about ETS exposure were not included in the interview until 1978 and the questions were changed in 1979. It is not known just how the questionnaire was changed, although the general tenor of the article suggests care in study planning and execution. The design for the larger study from which the ETS data are taken is pair-matched on numerous factors of potential interest, including "nonsmoking status," which contributes favorably to the analysis of ETS data alone. Cases with secondary tumors were excluded, histological type was considered, and all subjects were personally interviewed. It appears that only the currently married females were included in the question regarding exposure to spousal smoke, which alleviates the need to make some approximating assumptions regarding exposure of widows, single females, and so forth.

Two areas that may need to be addressed in the analysis of ETS subjects have to do with the definition of "ETS exposure" and "nonsmoker." The duration of smoking was comparable in cases and controls, but interview questions regarding exposure to ETS refer only to current exposure (this is not explicit in the article but was confirmed by the first author). Any effect from reliance on current exposure alone should be a bias toward the null hypothesis. Also, a measure of exposure in units (e.g., number of cigarettes per day or pack-years smoked by spouse) would make the question less subjective and help to dichotomize on ETS exposure more sharply. Because lung cancer may have a latency period of 20 years or so, exposure in the past, both in terms of duration and intensity, should be more meaningful than current exposure alone. With regard to the definition of nonsmoker, the requirement is less rigid than is often imposed. Ever-smokers are included provided they did not smoke more than the equivalent of 1 cigarette per day for 1 year (about 18 packs). It is difficult to know, however, what constitutes a "negligible" level of past smoking. Any bias from former smoking should inflate the relative risk, but that outcome appears unlikely in this study (RR = 0.74).

One of the factors of interest to the investigators is occupation, so cases and controls were not matched on that variable. For ETS exposure, occupation could be a confounding factor. Among females, the controls contain a higher percentage of professional and skilled workers than do the cases (47 to 25) and a lower percentage of housewives (41 to 50). Some differences are also apparent in religious preference between cases and controls that may bear some influence through lifestyle or dietary practices. Variables such as these may need to be taken into account in an adjusted analysis when more data become available.

A.4.18. KALA (Tier 1)

A.4.18.1. *Author's Abstract*

"A case-control study was undertaken in Athens to explore the role of passive smoking and diet in lung cancer, by histologic type, in nonsmoking women. Among 160 women with lung cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were lifelong nonsmokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed 120 were lifelong nonsmokers. Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% C.I. = 1.1, 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semiquantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (95% C.I. = 0.10, 0.74). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma."

A.4.18.2. *Study Description*

This study was undertaken in Athens, Greece, in 1987-89. It sought to explore the role of passive smoking and diet in the causation of lung cancer in nonsmoking women. All data used in the study were collected specifically for that purpose.

Cases are never-smoking women hospitalized in one of seven Greater Athens area hospitals during an 18-month period of 1987-89 with a definite diagnosis of lung cancer from histologic, cytologic, or bronchoscopic exam. Controls were selected from female never-smoking patients in the orthopedic ward of the same seven hospitals and an orthopedic hospital. A control was interviewed within 1 week of a corresponding case, thus essentially density-sampled but otherwise unmatched. Cases were not specifically restricted to incident cancers. All subjects were interviewed face-to-face by one of five trained interviewers; interviews apparently were unblinded. A total of 160 lung cancer cases and an equal number of controls were initially identified; 6 cases and 12 controls were too ill to interview, whereas 3 controls and no cases refused to participate. After exclusion of smokers, 91 cases and 120 controls remained. The age distributions of the cases and controls are very similar: for cases (controls), 16.5% (14.2%) were less than 50 years of age, 19.8 (18.3%) were 50 to 59, 29.7 (25.8%) were 60 to 69, and 34.1 (41.7%) were 70 or older. Current residence, level of education, occupation (housewife vs. other) and marital status were also similarly distributed between cases and controls. Case diagnosis was established by histology (48%), cytology (38%), or bronchoscopy (14%), with exclusion of cancers diagnosed as secondary.

Persons reportedly smoking fewer than 100 cigarettes in their lifetime are classified as nonsmokers. No mention is made of pipe or cigar smoking. Several different sources of ETS exposure are considered: husbands who smoke quantified in terms of years exposed and average number of cigarettes smoked per day; household members other than husbands who smoke, quantified by the sum of years exposed to each smoker; and coworkers who smoke, measured by the number of smokers sharing the "same closed space" as the subject. Presumably, childhood exposure is included in the household exposure assessment. For spousal smoking, single women are considered unexposed, whereas exposure of widowed or divorced women is based on the period when they were married. No attempts to verify exposure are mentioned.

For analysis of husband's smoking based on cigarettes per day, 64 out of 90 (exposed/total) cases and 70 out of 116 controls gives a crude odds ratio of 1.6 for 90 cases and 116 controls; 64 cases and 70 controls were exposed. The authors present results stratified by four exposure categories, which indicate no significant association ($p = 0.16$). Crude data for husband's smoking stratified by five levels of smoking duration (never, < 20, 20-29, 30-39, and 40+ years) yield a marginally significant increase in association with increasing duration ($p = 0.07$), with odds ratios of 1.0, 1.3, 1.3, 2.0, and 1.9, respectively. No statistically significant association was noted for ETS exposure from other household members ($p = 0.60$) or for exposure at work ($p = 0.13$), but the crude odds ratios for these exposures were 1.41 and 1.39, respectively. Stratification by level of intake for each of 16 food and nutrient groups yielded a significant negative (favorable) association with cereals ($p = 0.04$) and a possible association with fruits ($p = 0.11$).

Multiple logistic regression was then used to adjust results for age, education, and interviewer. An adjusted relative risk estimate of 1.92 (95% C.I. = 1.02, 3.59) was obtained for marriage to a smoker. After adjustment, trends for estimated lung cancer risk showed an increase with duration of exposure (average 16% per 10 years) and packs per day (6% per pack), but these were not statistically significant. No trend was observed for ETS in the household or workplace. Adjustment for other sources of air pollution had no effect on the analyses. Adjustment of dietary analyses for age, education, interviewer, and total energy intake indicated a significant decrease in estimated risk between highest and lowest quartiles of consumption of fruit (RR = 0.33; $p = 0.02$) and a nearly significant increase with consumption of retinol (RR = 1.31; $p = 0.06$), whereas beta carotene (RR = 1.01) and other dietary factors had no significant effect. Adding fruit consumption to the model for passive smoking increased the adjusted relative risk for husband's smoking slightly, from 1.92 to 2.11. Stratification by lung cancer cell type yielded somewhat lower adjusted estimated relative risks for adenocarcinoma (2.04) than for squamous, small, and large cell cancer combined (2.58). No adjusted results were presented for other household or workplace exposure.

The authors' conclusion is best reflected in their abstract (shown in full above). Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1. Number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data indicated that high consumption of fruits was inversely related to the risk of lung cancer. Neither vegetables nor any

other food group had an additional protective effect. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

It is noted that these findings are compatible with the relatively low incidence of lung cancer in the Greek population--a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.

A.4.18.3. *Comments*

This study was generally well designed and executed. Set up specifically to address passive smoking and diet as etiological factors in lung cancer, it includes sufficient numbers of nonsmoking women to produce substantive results. Interviews were face-to-face, and no proxies were used, enhancing accuracy and comparability of responses, whereas the very low rate of refusal minimizes potential bias due to volunteer selection. Cases and controls were very similar demographically, were drawn from most of the same hospitals, and were matched temporally on time of interview, so comparability seems high. Furthermore, the study hospitals' patient population accounts for the majority of lung cancer and trauma patients seen in the Athens area, enhancing generalizability of results. Most lung cancers were histologically or cytologically confirmed, reducing chances for misclassification of disease status.

On the debit side, the apparently unblinded interviews could have been biased (although what can be accomplished toward that end is limited). Adjustment for interviewer in the analyses did not affect the results, however, and it is unlikely that all interviewers would share the same bias. Determination of what constitutes workplace exposure is vague, and childhood exposure is not clearly differentiated from adult household exposure; these were notably the passive smoking categories, which showed the least association with lung cancer. ETS exposure in the workplace is analyzed with regard to trend (Table 2), with levels of exposure represented by "housewife" (zero exposure), "minimal," and "some," resulting in a p value of 0.13. Perhaps correctly, the authors cautiously note the evidence that ETS exposure is associated with increased risk (referring to Table 2 in general, not just exposure at work) but indicate that the differences are not large enough to be interpretable without controlling for other factors. An analysis of exposed versus unexposed for the workplace may have been useful, especially an adjusted analysis. Our calculation of the crude odds ratio for a comparison of "minimal" and "some" exposure at work is 1.7, which is suggestive.

Methodological rigor and thoroughness are particularly evident in the treatment of other factors that may affect risk. Despite the demographic similarity of cases and controls, the key demographic variables of age and education were nevertheless controlled for in the analyses, along with interviewer identity. The potential effects of air pollution, total energy intake, and other dietary factors on lung cancer incidence were examined, and the impact of cancer type was evaluated. An association of husband's smoking with lung cancer yielding an odds ratio of around 2 persisted with adjustment for those factors. The authors claim to have taken special effort to exclude ex-smokers from misclassification as never-smokers, taking account of this potential source of upward bias. No discussion was found,

however, of what measures were taken to control misclassification of former smokers as never-smokers, beyond interviewing subjects about current and former smoking habits.

In summary, this study presents evidence of a level- and duration-dependent association between husband's smoking and lung cancer in a well-defined and highly comparable group of Greek cases and controls. Positive but nonsignificant relationships with general home or workplace passive smoking were observed, and there are indications that additional analysis of workplace exposure may be worthwhile. No effect of air pollution was observed. With regard to dietary factors, the large number of potential factors considered raises the issue of multiple comparisons. Fruit consumption may be a significant factor, but further evidence is needed to firmly establish this, particularly in view of the number of dietary factors explored. Dietary factors, however, do not account for the results for ETS exposure in this study. The results regarding spousal smoking cannot be readily attributed to bias, and they provide good quantitative data on the issue of passive smoking and lung cancer. This well-conducted study makes a valuable contribution to the evidence on lung cancer and ETS exposure.

A.4.19. KATA (No tier assignment is made on this study because the OR is undefined.)

A.4.19.1. *Author's Abstract*

"It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis has become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women."

A.4.19.2. *Study Description*

This study was undertaken in the Nara Prefecture, Japan, to investigate the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women. Active smokers are included in the study, from which the nonsmokers are drawn for analysis. Matching is retained, however, in the nonsmokers.

For the whole study, subjects were drawn from a hospital (presumably the Nara Prefecture Medical University Hospital) during an unspecified period of time. Cases are female patients with histologically diagnosed lung cancer; controls are female patients with "nonmalignant" disease, matched 2 to 1 with cases on age plus or minus 2 years. It is not clear if only incident cases were used and if controls were density sampled. Case diagnoses were obtained from histological exam results, whereas control diagnoses were presumably from medical charts. Other

information was collected from apparently unblinded "questioning," with an unspecified degree of reliance on proxy responses from family members.

A total of 25 cases and 50 controls are included in the study; no information on refusals is provided. Exclusion of active smokers leaves only 17 cases and, with retention of 1:1 matching, 17 controls. Mean ages for the total study population are 67.5 ± 8.8 years (67.6 ± 8.5 years) for cases (controls). The age distribution of ETS subjects is not discussed. Nonsmokers are defined by exclusion of "active smokers," with no delineation between former and current smokers. ETS exposure is defined as exposure to smoking more or less daily through living with a smoker. Three periods of ETS exposure are considered: current, past, and childhood, the last for those "exposed since early childhood." Clearly these types are not mutually exclusive, although current sources of exposure are omitted from the "past" exposure category, even if present for a long time.

ETS exposure is quantified as cigarettes per day smoked times number of years. No mention is made of cigar or pipe smoking, nor of checks on exposure data. No distinction is made regarding marital status. Tumors occurring among current passive smokers were mostly adenocarcinomas (13/17), the remainder (4/17) being squamous or small cell cancers. Airway proximity was not specified. Excluding active smokers, all 17 cases were current passive smokers, compared with 14 out of 17 controls, for an odds ratio of 1.2, whereas past passive smoking characterized 16 of 17 cases and 17 of 17 controls, for an odds ratio of 0.9 (these odds ratios reflect the substitution of 0.5 for 0 in the exposure categories in which no subjects fall). Childhood passive smoking was reported in 13 of 15 cases and 7 of 15 controls (apparently all those for whom information was available), for an odds ratio of 7.4 ($p < 0.1$). None of the passive smoking odds ratios was statistically significant at the 5% level. No definite conclusion can be drawn from the present study, but there is a suggestion that passive smoking is associated with development of lung cancer in the Nara region. The effect of passive smoking that continued to the present time was especially marked, particularly in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, an effect of passive smoking in the past is suspected. Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, is apparent.

A.4.19.3. *Comments*

The histological diagnosis of all cases, in combination with the apparent involvement of the researchers in the diagnoses, virtually eliminates the potential pitfall of misclassification of lung cancer cases. It also allows specific breakdowns by cell type. With regard to passive smoking, however, limitations related to exclusion of active smokers greatly reduced the study's potential.

In their initial analyses, the authors investigate passive smoking without excluding or stratifying on active smoking and report statistically significant associations with lung cancer and combined effects with family history of cancer. This is not a meaningful analysis, because the effects of active and passive smoking cannot be separated and passive smoke exposure probably correlates strongly with extent of active smoking. Excluding active smokers greatly

reduces the available numbers of matched subjects and, in combination with the very high exposure prevalence among qualifying controls, makes the differences between cases and controls highly unstable for all comparisons except for that of childhood exposure. Even here, with an estimated relative risk of 7.4, the results do not reach the 5% level of statistical significance, notwithstanding the problem of multiple comparisons. The authors also conduct cell-type-specific analyses, but these too fail to yield significant results. The extraordinarily high proportion of exposed present and past passive smoking controls is apparently a fluke, because the proportion is not as high in the total control subject population (or childhood passive smoking controls). Nevertheless, exposure was very common among controls. This indicates that the exposure criteria may be too lax or, alternatively, that the control population included a substantial proportion of persons with smoking-related diseases (controls being only stipulated not to have malignant disease).

In light of the minimal utility of the study's passive smoking analyses, detailed consideration of design strengths and weaknesses is unwarranted. Major points not already mentioned relate to information ascertainment and confounding. Interviews were apparently unblinded and, especially if conducted by the authors themselves, may thus have been biased toward uncovering exposure among cases (although the high prevalence of exposure among controls as well as cases argues against this). Furthermore, the extent of proxy interviews, potentially decreasing accuracy of exposure assessment, is unclear.

All subjects are female and, although results are not age adjusted, matching on age was retained for all analyses. No other risk factors except family history of cancer were considered, probably due to limited subject numbers, because much information on other factors was collected. Moreover, family history was considered only in the nonmeaningful analyses, which did not differentiate active and passive smokers. Thus, although the problems with numbers and exposure misclassification probably reduced the study's ability to detect whether an association exists, information bias and confounding could have biased results either up or down.

In summary, this study's data are consistent with an association of passive smoking, particularly childhood exposure, with lung cancer, but the results are too unstable and subject to potential bias to carry much weight, and the quantitative results must be viewed with extreme caution.

A.4.20. KOO (Tier 1)

A.4.20.1. *Author's Abstract*

"Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. When relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that

peripheral tumors in the middle or lower lobes (or less strongly, squamous or small cell tumors in the middle of lower lobes) had increasing relative risks that might indicate some association with passive smoking exposure."

A.4.20.2. Study Description

This study, the second of four from Hong Kong, is based on a secondary data set of reported female never-smokers. The parent study from which the data on ETS subjects were drawn includes ever-smokers in a matched case-control study of 200 cases and 200 controls (Koo et al., 1984; also see Koo et al., 1983). Its objective is to assess the role of passive smoking as a potential etiological factor in the high incidence rate of lung cancer among Chinese females in Hong Kong. The current article emphasizes the quantitation of lifetime ETS exposure and the histological profile of lung cancer in exposed never-smokers.

In the parent study, cases are from the wards or outpatient departments of eight hospitals in Hong Kong during 1981-83. Controls are healthy subjects from the community, matched on age (within 5 years), district of residence, and type of housing (public or private). The cases are incident, and control sampling is density. Attrition due to selection or followup totals 26 (8 too ill to interview and 18 with secondary lung cancers), leaving 200 cases for interview. Face-to-face interviews of 1.5 to 2 hours were conducted directly with cases and controls. There was no restriction of cases by cell type of lung cancer. The ETS subjects extracted from the parent study include 88 cases and 137 controls. Of the 88 cases, 83 were confirmed by histology and 5 were "confirmed malignant." The number of squamous cell and small cell cases combined is 32 (23 ETS exposed; 72%); the corresponding figure for adenocarcinoma and large cell combined is 44 (31 ETS exposed; 70%); 12 cases are of another cell type or otherwise unspecified. For the 86 cases with available information, tumors were centrally located in 37 (25 ETS exposed; 67%) and peripherally in 46 (34 ETS exposed; 74%).

The term "never-smoker" applies to persons who have smoked a total of fewer than 20 cigarettes. Interview questions regarding exposure to ETS include cigarette and cigar smoking in the home during childhood, by the spouse and other cohabitants in adulthood, and workplace exposure. "ETS exposed" is technically used in several ways. For the comparison of exposed with unexposed ever-marrieds, it means the husband ever smoked in the wife's presence. For measures of exposure in terms of duration or rate (e.g., total years, hours/day, total hours, and cig./day), there is some variation. For example, total years of exposure is derived by adding the years during which tobacco exposure occurred in the home or workplace. The total hours of exposure are calculated by multiplying the average hours per day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. The mean hours per day of exposure are found by adding the hours per day of home and workplace exposures and dividing this figure by the age of the subject. This figure is intended to approximate the average number of hours of exposure per day experienced by the subject, over her lifetime. Cumulative exposure is estimated by the total cigarettes smoked by family members, weighted by years of exposure.

When data are analyzed on the simple basis of whether a husband ever smoked in the presence of the wife, the crude and adjusted odds ratios are 1.55 (95% C.I. = 0.94, 3.08) and 1.64 (95% C.I. = 0.87, 3.09), respectively.

The crude analysis applies to ever-marrieds only, which excludes three subjects. An adjusted analysis uses cigarettes per day smoked by the husband as the measure of ETS exposure. Conditional logistic regression was applied with stratification on district of residence, and housing type (public/private); model parameters were included for age, family history of lung cancer (yes/no), number of live births, and number of years since exposure at home or in the workplace.

The crude and adjusted methods give very similar odds ratios and confidence intervals, but the tests for trend differ substantially. The test for trend on the crude data is based on the Mantel-Haenszel test, using midpoints of the intervals for cigarettes per day smoked by the husband; the significance value is $p = 0.10$. The p value for trend in the adjusted analysis is 0.32. For analysis of data by other measures of exposure, as described above, the estimated odds ratio ranges between 1.0 and 4.1 across the three levels of the various measures of ETS exposure for both the analyses of the crude data and the adjusted analyses by conditional logistic regression, with two exceptions from analysis of the crude data for hours per day of exposure. The results are not statistically significant in most cases, because the sample sizes at each exposure level are small. The dose-response patterns observed are clearly sensitive to the measure of ETS exposure used, with several exhibiting an apparent peak at a low exposure level. Although the authors acknowledge that it was troubling to find the lack of a response pattern, no further explanation is given.

The authors did not detect a significant trend in the crude or adjusted odds ratio for the four lifetime measures of passive smoking (total years, hours, mean hours/day, cig./day). Although the odds ratio for the intermediate level exposures of hours per day and cigarettes per day was significant, the odds ratio at the highest levels of exposure for these two variables fell to a nonsignificant 1.0 to 1.2. In fact, the odds ratio for the highest exposure levels for three out of the four measurements were below all of those with lower exposures and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted odds ratios were greater than 1.0. Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cig./day) by mean hours per day of exposure, also did not indicate a dose-response relationship. The analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher odds ratios.

It is concluded that when the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small cell tumors in the same lobes, exhibited better odds ratio patterns for passive smoking in terms of consistency, strength, and dose response. The odds ratio for total years, hours, and hours per day measurements of squamous and small cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted odds ratios for adenocarcinoma or large cell lung cancers.

The cases are divided into two groups histologically, those with squamous cell or small cell tumors and those with adenocarcinoma or large cell malignancies. Although none of the crude or adjusted analyses are found to be significant, it is concluded that an observed dose-response pattern seems to be more apparent in the squamous or small

cell group. With regard to tumor location, some evidence suggests that peripheral tumors in the middle or lower lobes may be more common in passive smokers.

A.4.20.3. *Comments*

As described above, the data employed in the current study were taken from a larger retrospective study of female lung cancer in Hong Kong (Koo et al., 1984) that matched 200 cases and controls on age, district of residence, and housing type (private or public, an indication of socioeconomic status). Attention to detail and accuracy is evident in most aspects of the parent study. In particular, considerable effort was put into attempting to ascertain a better quantitative measure of exposure than used in preceding studies of ETS. Records were apparently verified to the extent possible to cross-check the accuracy of information collected, cancers were verified histologically, and analyses investigated questions related to the histological types and sites of tumors that may be related to passive smoking.

The never-smokers from the parent study, 88 cases and 137 controls, compose the secondary data set on which the current article is based. The matching of the subjects, of course, is no longer assured, leaving the comparability of the two groups uncertain. In addition, 60 (27%) of the subjects are widows, with no information provided on the distribution between cases and controls. Because spousal smoking is typically the variable on which ETS exposure pivots, this may have some bearing on the response. However, an adjustment is made in some analyses for years since exposure to cigarette smoke ceased.

Some factors in the study itself may be contributing to the variable dose-response patterns. First, the number of ETS subjects is fairly small. When the subjects are classified into finer categories of exposure, the statistical variability is greatly increased (total of cases and controls is typically below 60). Second, questionable measurements of ETS may be causing some distortion. For instance, in the calculation of total years and total hours of ETS exposure, the years and hours were not added for simultaneous exposure to more than one smoker. Pipe smoking and the cigarette consumption levels of coworkers were excluded from the weighted average of the total cigarettes per day smoked by each household member. Thus, measurement appears to be based on the assumption that never-smoking women were exposed to ETS evenly throughout their lives (the authors claim that only subjects were used for which the exposure remained relatively regular during the lifetime, although no mention was found of cases being omitted because of failure to satisfy this criterion). Even if this assumption were valid, childhood and adulthood exposures are mixed as if the effects of exposure are interchangeable. Interestingly, differences between exposure in childhood and adulthood is one of the questions addressed in the article.

Although the objective is worthy, the attempt to quantitate exposure more precisely than previous studies appears to obscure more than to clarify. Some assumptions are not made very explicit, and their potential implications are not addressed well, which leaves some uneasiness about the conclusions. The authors have published at least three articles before this study that have some bearing on passive smoking and lung cancer, but their results are not discussed in the current study, even when the data analyzed are from the same source (Koo et al., 1983, 1984, 1985).

Those articles, one of which describes the parent study (the 1984 citation), appear to reach somewhat different conclusions from this study regarding the predominance of histological type associated with passive smoking. Putting the current study's conclusions within the context of related prior work would enhance their clarity and interpretation.

Considering the reservations described above, the suggestion that the evidence indicates some association of passive smoking with the *location* of tumors is an overinterpretation of the data. A weaker conclusion is warranted, namely, that ETS exposure is associated with increased lung cancer incidence. What may be of most value in this study is the analysis based on the dichotomous classification of cases and controls as exposed or unexposed based on spousal smoking. Two concerns, however, will be reiterated. The ETS data are taken from a larger study not matched on smoking status, so they are unmatched. The study includes 80 widows, without mention of their distribution between cases and controls. In the adjusted analysis, an attempt is made to take into account the number of years since last exposure, which would require some assumption regarding the change of risk relative to cessation of exposure. Both of these concerns are mitigated, however, by the similarity of the odds ratios and confidence intervals for the unadjusted and adjusted analyses. The care and thoroughness of the study in general make the results on the odds ratio for exposure to spousal smoke a useful contribution for evaluation with other study outcomes.

A.4.21. LAMT (Tier 2)

A.4.21.1. *Author's Abstract*

"In a case-control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighborhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk in ever-smokers was 3.81 ($p < 0.001$, 95% C.I. = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never-smoking women, RR for passive smoking due to a smoking husband was 1.65 ($p < 0.01$, 95% C.I. = 1.16, 2.35), with a significant trend between RR and amount smoked daily by the husband. When broken down by cell types, the numbers were substantial only for adenocarcinoma (RR = 2.12, $p < 0.01$, 95% C.I. = 1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked."

A.4.21.2. *Study Description*

This hospital-based case-control study was conducted in Hong Kong during 1983-86, to investigate whether smoking is a major risk factor for lung cancer in Hong Kong Chinese women and, if so, to determine the relationship between smoking and the histological types of lung cancer. Both active and passive smoking are of interest. The ETS subjects constitute only a subset of the whole study because it includes active smokers.

Eligible cases for the whole study are the 445 female patients with pathology-verified lung cancer admitted into eight large hospitals in Hong Kong during 1983-86. Cases were interviewed in person. Only a few eligible

patients declined or were too ill to cooperate. An equal number of healthy neighborhood controls were identified and interviewed by density sampling. Controls were matched to cases on sex, age (± 5 years), and place of residence. The cases and controls include both never-smokers and ever-smokers, but smoking status was not used in matching.

"Never-smoker" means a person who never smoked as much as one cigarette per day, or its equivalent, for as long as 1 year.

A woman is "ETS exposed" if her husband smoked for at least 1 year while they lived together. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. No information was collected on ETS exposure from other household members' smoking or smokers at work. Single (never-married) women were classified as nonexposed (6.8% and 5.2% in cases and controls, respectively). The treatment of widowed and divorced subjects is not explicitly addressed. Age and place of residence, as well as a series of other demographic variables, are similar between cases and controls.

The distribution of lung cancer by cell type in ETS cases is as follows: squamous cell, 12 of 27 (number exposed/total); small cell, 6 of 8; adenocarcinoma, 78 of 131; large cell, 7 of 9; and others or unspecified, 12 of 24. The corresponding crude odds ratios and 95% confidence intervals are 0.85 (0.35, 2.06), 3.00 (0.53, 16.90), 2.12 (1.32, 3.39), 3.11 (0.50, 19.54), and 1.08 (0.41, 2.82), respectively. The odds ratio for all cell types combined is 1.65 (1.16, 2.35), based on 115 of 199 (exposed/total) cases and 152 of 335 controls. The data for all cell types together, and for adenocarcinoma alone, are both significant at $p < 0.01$. No information is available on the airway proximity of tumors.

Trend tests were conducted for the amount smoked daily by the husband, categorized in terms of cigarettes as "nil," 1 to 10, 11 to 20, and 21 or more. The odds ratios in the three exposure categories are 2.18, 1.85, and 2.07, respectively, when all cell types are included. For adenocarcinoma alone, the corresponding odds ratios are slightly higher (2.46, 2.29, and 2.89, respectively). The dose-response relationship does not appear to increase between the lowest dose and the highest dose, but a test for trend is significant ($p < 0.01$ for all cell types and $p < 0.001$ for adenocarcinoma alone) when the "nil" group is included. No adjusted analyses are given.

The authors conclude that the significant trends observed between relative risk and amount smoked daily by husband, for all cell types combined and for adenocarcinoma alone, support the view that the observed association between ETS exposure and lung cancer is likely to be causal.

A.4.21.3. Comments

This study is the fourth of the Hong Kong epidemiologic inquiries into tobacco smoke as a possible etiological factor in the high rate of lung cancer, particularly adenocarcinoma, among women. Active smoking was included as well as passive smoking because the previous studies in Hong Kong were inconclusive. According to the authors, this led to the hypothesis that smoking is not a risk factor for adenocarcinoma in Hong Kong Chinese women. Matching of controls to cases was conducted for the whole study, including active smokers. It cannot be

assumed, however, that the never-smokers alone, who constitute 45% of the cases and 76% of the controls, are matched.

Overall, the study demonstrates care in planning and execution. The sample size of ETS subjects is moderately large, providing higher statistical power than the previous Hong Kong studies. All cases were pathologically confirmed as primary lung cancers, essentially eliminating the potential for error due to disease misclassification. Odds ratios were calculated by histological type for comparison. Cases and controls were interviewed personally, apparently with no proxy respondents and very few refusals, which reduces the potential for response bias. The exclusive use of incident cases helps to control potential selection bias, and density sampling of controls contributes to comparability of cases and controls. For the whole study, including smokers, healthy controls were matched to cases by sex, age, and neighborhood of residence. The mean and standard deviation of ages are nearly identical in cases and controls. According to the authors, a comparison by other demographic variables showed that, for the whole study, cases and controls were also comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Further attention to detail is evident in the clear definitions of "never-smoker" and "ETS exposure," essential to accurate classification of subjects for analysis and interpretation. Single women were treated as not exposed to husband's smoking, which could be a source of bias because these women may be exposed from other household members. This possibility was considered, however, because the article reports that similar results were obtained when single women were excluded.

In summary, the crude odds ratios vary between 2.1 and 3.1 for small cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma significant at $p < 0.01$. The odds ratios are consistently elevated at all three intensity levels of spousal smoking, varying between 1.8 and 2.9, with the odds ratio for adenocarcinoma alone somewhat higher than for all cell types combined. There is no apparent upward trend, however, from the lowest smoking intensity (1-10 cig./day) to the highest (21+ cig./day). These statistical results are ostensibly suggestive of an association between ETS exposure and lung cancer incidence, but they are based on only crude data with cases and controls unmatched, even on ages. Nor are statistical methods used that could adjust for matching variables, or other factors, in the data analysis (e.g., by stratification or logistic regression). Although this study was carefully conducted in most respects, the disregard for potential confounding effects leaves the authors' conclusion uncertain.

A.4.22. LAMW (Tier 3)

(Note: This study is part of the thesis of LAM Wah Kit submitted to the University of Hong Kong for the M.D. degree in 1985, entitled *A Clinical and Epidemiological Study of Carcinoma in Hong Kong*. The description given below is from Chapter 7 of the thesis only, entitled *Case-Control Study of Passive Smoking, Kerosene Stove Usage and Home Incense Burning in Relation to Lung Cancer in Nonsmoking Females (1981-84)*, which the author submitted in response to our request. The abstract below was prepared by the reviewers, since none was available from the author.)

A.4.22.1. Abstract

The study's objective is to investigate the hypothesis that an inhaled carcinogen may be related to the high incidence of centrally situated adenocarcinoma of the lung observed in nonsmoking female patients. Air pollution is probably not an important factor because it presumably affects both men and women. Most women in Hong Kong either stay at home or join the work force in commerce, services, or manufacturing, which are not associated with any known risk factor for lung cancer. Three etiological activities, all predominantly in the home, are considered in this study: passive smoking, kerosene stove cooking, and home incense burning. No evidence was found to implicate exposure to kerosene stove fumes or incense burning in centrally located adenocarcinoma. There is suggestive evidence of an association between ETS exposure from smoking husbands and occurrence of peripheral (but not central) adenocarcinoma. Why the location tends to be peripheral instead of central is speculative.

A.4.22.2. Study Description

(*Note:* The details of the study are not complete in the material provided. Some useful information, however, is available.)

The cases are all of the Chinese female patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984 with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types. Care was taken to exclude patients with secondary carcinoma of the lung; otherwise, all patients were included. The controls are Chinese female patients admitted to the orthopedic wards of the hospital in the period 1982-84, comparable to lung cancer patients in age and social class. Patients with pathological fractures due to smoking-related malignancies or with peripheral vascular disease-related orthopedic conditions were excluded.

Both cases and controls were patients of the third-class general wards, mostly from the lower income group. All subjects were interviewed in person. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking with kerosene, and home incense burning, in the form of a standardized questionnaire. For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, the next of kin was interviewed, with the patient as interpreter. The whole study, including active smokers, contains 161 cases and 185 controls, similar in age (median age is 67.5 [66] for cases [controls]), socioeconomic status (as measured by occupation and years of schooling), and recent residence. The author considered it unnecessary to stratify on these or any other variables.

The ETS subjects consist of 75 (144) cases (controls), including 16 (14) never-married cases (controls). The distribution of cases by cancer cell type is as follows: squamous cell (7), small cell (3), large cell (5), and adenocarcinoma (60). Questions related to ETS exposure include details on each smoker in the home (husband, others, mother, and father), amount smoked per day, hours of ETS exposure per day, and number of years smoked. Information about exposure in the workplace includes size of the workplace, number of coworkers who smoke, exposure time/day, and number of years of exposure at work.

Only the data for adenocarcinoma, the predominant cell type observed and the pathogenesis of interest, are analyzed. The number of cases is 37 out of 60 (exposed/total), and the number of controls is 64 out of 144, where ETS exposure refers to spousal smoking. The odds ratio (calculated by the reviewers) is 2.01 (95% C.I. = 1.09, 3.72). The author divides the cases by location according to airway proximity, with 18 of 32 (exposed/total) located centrally and 19 of 28 in peripheral regions. The respective risk ratios are 1.61 and 2.64. Two tests were conducted for significance, including the Bayesian risk ratio analysis and a test of the slope for the exposure parameter in a simple logistic regression model. The significance levels are 0.11 and 0.19, respectively, for the central location and 0.01 and 0.02, respectively, for peripheral tumors. The test results differ widely for total passive smoking (home or workplace). For the central location, the respective significance levels are 0.09 and 0.3; for peripheral locations, the corresponding values are 0.03 and 0.15. It is suggested that the different outcomes for the two tests applied to total passive smoking may be due to a nonlinear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information. The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumors) in the cases was unexpected. Based on the available raw data, exposure to a smoking spouse, cohabitant, and/or coworker is associated with an odds ratio of 2.51 (95% C.I. = 1.34, 4.67) for all cell types combined. The author concludes that there is a suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking attributable to smoking husbands. Kerosene and incense burning were not found to be associated with adenocarcinoma, either central or peripheral.

A.4.22.3. Comments

Cases and controls appear to be comparable in age, socioeconomic status, and recent residence for the whole study (including active smokers), although the study design is not matched on these or other variables. Some discrepancies between cases and controls are apparent, however, such as a higher percentage of cases than controls working outside the home (41% compared with 28%). The figures for nonsmokers alone (i.e., the ETS subjects) are not given, so comparability is uncertain for analysis of ETS exposure. Care has been taken to include only primary lung cancer patients among the cases, essentially eliminating this potential source of bias. Subjects were personally interviewed, with apparently only a small number of proxy respondents required, although no figure is given. The interviews apparently were not blinded, but that may not have been feasible considering the nature of the questions asked and the use of noncancer patients as controls. Considerable attention is given to histological type of cancer and the location in terms of airway proximity.

The author is particularly interested in the etiology of adenocarcinoma and focuses discussion on the adenocarcinoma cases to the exclusion of others. Although the raw data pertaining to other cell types are tabulated, more attention to those types in the analyses would have been useful. The adenocarcinoma cases are categorized further by central and peripheral location, which are analyzed separately. Again, a combined analysis would be useful (the reviewers calculated the crude odds ratio for the combined data, which is given above). Although logistic regression is employed as one of the two statistical tools for analysis, factors that may differ between cases and

controls are not included. Potential confounding variables need to be controlled for, by logistic regression, poststratification, or otherwise. To claim that cases and controls are similar in potential confounding characteristics does not alleviate the need to adjust for them in the analysis, particularly when the ETS data are a subset of the larger data set to which reference is made. Similarly, in testing three factors for an association with lung cancer (passive smoking, cooking with kerosene, and burning incense), it would be useful to conduct an analysis that will allow evaluation of the effect of each after adjustment for the other two.

The suggestive evidence that passive smoking is more likely associated with adenocarcinoma in peripheral rather than central locations may be logical but is weak, especially considering the lack of analytical rigor. The proportion of ETS-exposed cases of adenocarcinoma is 18 of 32 (56%) for central locations and 19 of 28 (68%) for peripheral locations. This difference is not statistically significant ($p = 0.26$ by Fisher's exact test). Consequently, the "apparent association" between passive smoking and peripheral adenocarcinoma (and not central tumors) may well be due to chance alone. There is suggestive evidence in the data that passive smoking may be associated with lung cancer ($OR = 2.01$, $p < 0.03$ for a one-sided test), but that is based only on the crude odds ratio in unmatched data and needs to be confirmed by a more thorough evaluation of the data that takes potential confounders into account. Overall, this study provides some suggestive evidence for an association between passive smoking and lung cancer. Potential confounders (including age) have not been controlled for, however, so attribution of the elevated odds ratio to ETS exposure is uncertain.

A.4.23. LEE (Tier 2)

A.4.23.1. *Author's Abstract*

"In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong nonsmoking lung cancer cases and of two lifelong nonsmoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in the hospital or not.

Among lifelong nonsmokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischemic heart disease, or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all."

A.4.23.2. *Study Description*

This study was undertaken in England, essentially from 1979 to 1983. Its stated objective is to investigate the relationship between passive smoking and risk of lung cancer in nonsmokers. It is an outgrowth, however, of a

hospital-based case-control study to assess whether the risk of cardiorespiratory disease associated with smoking varies by type of cigarette smoked. It was initiated in 1977 in 10 hospital regions in England. In 1979, interviewers began gathering information on passive smoking as well in four of the regions. Then in 1982, this case-control study of the effects of passive smoking was begun using nonsmoking cases identified by the ongoing cardiorespiratory effects study. For the new study, spouses of cases and specially selected controls were interviewed regarding smoking habits. Previously collected data on passive smoke exposure obtained from patients back to 1979 were used.

Basically, two substudies were conducted. One used the data obtained directly from hospitalized cases and controls to address several sources of passive smoke, including spousal (henceforward the "passive smoking" study); the second substudy used data obtained from the spouses of cases and controls along with corresponding information from the patients themselves, when available, to address spousal smoke exposure only (henceforward the "spousal smoking" study). Cases for the passive smoking study were currently married lifelong nonsmokers diagnosed with lung cancer (of any cell type), chronic bronchitis, ischemic heart disease, or stroke in one of four participating hospital regions. Controls were currently married lifelong nonsmoker inpatients diagnosed with a condition definitely or probably not related to smoking and individually matched on sex, age, hospital region, and, when possible, hospital ward and time of interview. Thus, density sampling was used when possible. For the spousal smoking study, previously married patients were excluded; the same criteria otherwise applied, except that controls were now matched on sex, age decade, and--as far as possible--hospital and time of interview.

Diagnoses were obtained from medical records. Exposure data were obtained through apparently unblinded, presumably face-to-face interviews with inpatients and their spouses. A total of 3,832 married cases and controls were interviewed regarding passive smoking through 1982; it is unclear how many potential subjects refused or died before interview. Only 56 of these were married lung cancer cases meeting the spousal smoking study criteria. Spousal interview data were obtained for 34 of these cases and 80 controls; interviews were refused by the remainder. Although matching of cases and controls was initially carried out, it was not retained in the analysis, and no demographic comparison of cases and controls used in the analyses is provided. Diagnoses were apparently drawn from patients' charts; provisional diagnoses were used where no final diagnosis was specified, no data on diagnostic technique(s) or histology was presented, and no diagnostic verification was reported.

The patient population consists of never-smokers, defined as lifelong nonsmokers, which presumably excludes cigar and pipe smokers. Exposure to ETS is approached in several ways. The primary exposure is that of a spouse smoking manufactured cigarettes at some point over the course of a marriage. Spousal smoking in the 12 months before interview also was assessed. In addition, "regular" exposure to passive smoke in various situations (i.e., at home or work, during travel or leisure) was assessed. The first two exposures were quantified in numbers of cigarettes smoked per day, the others in terms of "not at all, a little, average, or a lot." Thus, it appears that cigar and pipe smoking may not have been included in the spousal smoking exposures. Comparison of individual responses regarding spousal smoking status by patients and their spouses revealed a high degree of concordance (97%) for

smoking during the past 12 months and a substantial concordance (85%) for smoking during marriage. No other checks on exposure data were reported.

The ETS patient data set includes 56 cases and 112 controls who met the initial study criteria. Not all of these answered each passive exposure question, however, and not all met the criteria for the spousal interview study. Similarly, spouses of 34 cases and 80 controls provided exposure information of varying completeness. Thus, the numbers involved in each analysis varied considerably. For smoking during marriage, data obtained directly from spouses indicated that for males and females combined, 24 of 34 lung cancer cases and 51 of 80 controls were exposed, which yields a crude odds ratio of 1.4 for spousal smoking. With standardization for age, an odds ratio of 1.33 (95% C.I. = 0.50, 3.48) was reported. Data obtained from qualifying patients, in contrast, revealed 13 of 29 cases and 27 of 59 controls to be exposed, yielding a crude *and* adjusted odds ratio of 1.00 (95% C.I. = 0.41, 2.44). Stratification by gender yielded adjusted odds ratios from spousal interview data of 1.60 (0.44, 5.78) and 1.01 (0.23, 4.41) for females and males, respectively, with corresponding odds ratios from patient interview data of 0.75 (0.24, 2.40) and 1.5 (0.37, 6.34). When spouses identified as smokers by interview with either source were classified as exposed, an odds ratio of 1.00 (0.37, 2.71) was obtained for female subjects. For the larger inpatient passive smoking study population, age-standardized odds ratios for passive smoke exposure at home, at work, during travel, and during leisure revealed no consistent associations, with as many negative as positive relationships observed after adjustment for both age and whether still currently married. The same inconsistency held true for spousal smoking during the last 12 months and during the whole marriage. Adjustment for working in a dusty job reportedly did not affect the conclusion that passive smoking was not associated with risk.

Spousal smoking was slightly negatively associated with chronic bronchitis, ischemic heart disease, and stroke, whereas a combined ETS exposure index was negatively associated with heart disease but positively associated with bronchitis and stroke.

The author concluded that the findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

A.4.23.3. *Comments*

The heart of this study is the spousal interview investigation of lung cancer and spousal smoking. Only 34 case spouses and 80 control spouses, and even fewer of the corresponding cases and controls themselves, are included, which gives the study low statistical power. Because the study began with hospital inpatient married lifelong nonsmokers, and matching on several key factors was employed, good comparability of cases and controls would seem readily achievable. No case-control demographics are provided, however, and matching is abandoned in the analyses. The occurrence of interview refusals and omitted responses (themselves a potential source of selection and information bias) may have contributed to the decision to abandon matching, with the aim of preventing further

substantial reduction in numbers through exclusion of unmatched subjects. As a result, the comparability of the cases and controls is uncertain. At least all are drawn from the same four hospital areas within a fairly limited timespan, which, in combination with the other study criteria, reduces the likelihood of serious noncomparability.

Numerous opportunities for misclassification of disease and exposure status are present. Current working diagnoses are apparently drawn from patient charts without verification, and controls are selected from patients with diagnoses judged either probably or definitely not associated with smoking by unspecified criteria. This creates considerable potential for misclassification, both through inaccuracies in diagnoses generally and through inclusion of smoking-related diseases in the control group particularly, which would produce a downward bias in results. Exposure misreporting and recall problems would seem least likely where spouses are interviewed directly about exposure within the past 12 months. Results for this situation are not presented, although they are reportedly similar to those for smoking during marriage.

The larger inpatient study elicited smoking data from patients, and only for their *first* spouse for patients who had remarried; thus, exposure occurring in subsequent marriages is not addressed. In addition, no information on duration or level of smoking in marriage is used in any of the spousal smoking analyses. The most likely result of these problems is nondifferential misclassification resulting in a bias toward the null. For general estimated home, work, travel, or leisure exposure to passive smoke, rough quantification *is* attempted by having patients categorize their exposure as "not at all, a little, average, or a lot." By necessity, this is a very subjective evaluation, and people more acclimated to smoke and tolerant of exposure might well tend to characterize a given amount of exposure as less severe than would a person less tolerant of smoke who more actively avoids exposure. This tendency would produce a bias toward negative association.

Standardization for age and restriction of cases and controls to currently married lifelong nonsmokers should control the effects of age, marital status, or active smoking, although misreporting of current or former active smoking cannot be ruled out entirely. Dusty occupation reportedly had no effect on the larger inpatient study results. Potential effects of race, socioeconomic status, diet, cooking habits, or any additional factors were not addressed.

One might expect the most accurate reporting of spousal smoke exposure when spouses are interviewed directly regarding their own smoking habits, and the most inadvertent misclassification when patients are queried about the smoking status of their first marital partner only. Analyses along these lines yielded slightly positive associations with smoking for the former and negative with the latter approach. No consistent pattern of association was seen for other sources and lung cancer, although high combined exposure scores were associated positively with chronic bronchitis and stroke and negatively with ischemic heart disease.

In summary, this study presents equivocal results that neither strongly confirm nor refute the hypothesis that passive smoking mildly increases risk of lung cancer. The quality of the study, however, is a limitation. The discrepant results for subject-supplied data (OR = 0.75) and spouse-supplied data (OR = 1.60), varying degrees of completeness of information on subjects, and the subjective nature of questions regarding ETS exposure limit confidence in the study's data and, consequently, the results of its analysis of those data.

A.4.24. LIU (Tier 4)

A.4.24.1. *Author's Abstract*

"In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analyzed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (OR = 7.37, 95% C.I. = 2.40, 22.66) and family history of lung cancer (OR 4.18, 95% C.I. = 1.61, 10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18, and 14.70), but not with passive smoking (OR 0.77, 95% C.I. = 0.30, 1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% C.I. = 2.86, 20.18), family history of lung cancer (OR 3.78, 95% C.I. = 1.70, 8.42), and personal history of cooking food (OR 3.36, 95% C.I. = 1.27, 8.88). In males, a dose-response relationship of lung cancer with smoking index (years of smoking/amount of smoking) was shown by risks of 1.00, 2.61, 2.17, and 4.70."

A.4.24.2. *Study Description*

This study was undertaken in Xuanwei County of China's Yunnan Province, a county whose lung cancer mortality rates are among the country's highest and wherein burning of smoky coal indoors in unventilated pits is a common practice. The study sought to assess "the influence of factors other than type of fuel on the occurrence of lung cancer in Xuanwei."

Cases of newly diagnosed lung cancer occurring among farmers at hospitals and clinics in Xuanwei between November 1985 and December 1986 were identified as potential study subjects. Up to five controls were identified for each case, depending on availability after matching on age (± 2 years), gender, and village of residence. A total of 112 cases were identified, from which 2 were excluded due to unknown addresses. Of 452 candidate controls, 26 were excluded due to erroneous questionnaire responses. All subjects were interviewed face-to-face by trained personnel using a standardized questionnaire, and blinding extended to both interviewers and interviewees.

The final study groups consist of 54 (56) female (male) cases and 202 (224) female (male) controls. Mean age is 52 years for both cases and controls, who are also similar in family size, ethnicity, birthplace, dwelling type, and type of fuel used (smoky coal, wood). Separate breakdowns for males and females are not provided. Very few of the cases (19/110 = 17%) were histologically or cytologically diagnosed, and no verification of diagnosis or exclusion of secondary tumors was undertaken (except to monitor mortality among some of the cases).

Exposure to ETS was not evaluated for males. Among females, only one subject (a control) reported ever having smoked, so the ETS population of females effectively consists of never-smokers. Subjects were classified as exposed to ETS if their household contained at least one smoker. Exposure is not quantified, and it is unclear whether former or only current exposure is intended. No checks on exposure status or consideration of marital status are mentioned, and no histological data are presented.

The proportion of exposed female subjects is 45 out of 54 (176/202) for cases (controls), yielding a crude odds ratio of 0.74. A conditional logistic regression analysis adjusted for other risk factors (presumably the other factors referred to are age-began-cooking and years-of-cooking) gives an odds ratio of 0.77 (95% C.I. = 0.30, 1.96). No further analyses of ETS exposure are provided.

Four non-ETS factors are significantly associated with lung cancer among females: family history of lung cancer (OR = 4.18; 95% C.I. = 1.61, 10.85), personal history of bronchitis (OR = 7.37; C.I. = 2.40, 22.66), age-began-cooking (OR = 2.44-1.03, but with a reversing and nonsignificant dose-response), and years-of-cooking (OR = 2.49-2.25, nonsignificant trend). Among males, significant positive associations were noted for total smoking index, often-cooking-own-food, family history of lung cancer, and history of chronic bronchitis, whereas age-began-smoking, years of smoking, and intensity of smoking showed modest but nonsignificant associations with lung cancer.

The authors conclude that "it is quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking" and "may also overwhelm the carcinogenic effect of passive smoking." "Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that those factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei."

A.4.24.3. Comments

This modestly sized study was not designed to test for effects of ETS exposure. Rather, it is a hypothesis-generating exercise aimed at covering a broad range of possible risk factors. Within that context, the study has considerable merit, but as an investigation of ETS it has numerous flaws.

Restriction to farmers minimizes concerns with occupation and overall lifestyle, and control selection, including matching on age, gender, and village, produced demographically comparable case and control populations for males and females combined despite the enigmatic exclusion criterion for controls. It is unknown, however, whether the groups remain comparable after subdivision into males and females.

The use of newly diagnosed cases reduces potential selection bias due to inclusion of prevalent cases, but the heavy reliance (83%) on clinical and radiological diagnosis and the absence of independent confirmation or exclusion of secondary tumors introduces a strong potential for misclassification of disease and precludes analyses by cell type. The observation that followup of a number of lung cancer patients revealed that almost all died within 6 months of

diagnosis does little to confirm diagnostic validity, contrary to the authors' interpretation. Such presumably random misclassification would make detection of an existing ETS-lung cancer association more difficult.

Exposure data collection procedures, particularly the exclusive use of face-to-face interviews without resort to proxies and the blinding of both interviewers and subjects, are laudable. For ETS, however, the exposure measure used is nonspecific and nonquantitative. Complications due to past exposure and differences in degree or duration could distort the observed disease-exposure relationship, probably biasing results toward no effect.

Potential confounding is not adequately addressed in the statistical analysis. The authors are particularly concerned with indoor smoky coal burning due to the known strong correlation between smoky coal use and lung cancer mortality in Xuanwei. Wishing to focus their investigations on factors other than smoky coal, they matched cases and controls on village, which "provided effective matching on fuel type." But because age and a host of other demographic factors, as well as smoky coal consumption, were comparably distributed in cases and controls (see study description), these factors were not considered further in the data analysis. This is a serious flaw, for pair matching was not retained in the analysis; thus, none of the above factors is effectively controlled for. The conditional regression analyses do control for risk factors other than those cited above, but exclusion of age, fuel type (e.g., smoky coal), and degree of exposure to fuel fumes may produce misleading results.

The presence of other significant risk factors for lung cancer makes detection of an effect from ETS, if present, less likely. Masking by the presence of smoky coal and other factors in the study environment is probably a factor in the remarkably weak association between active smoking and lung cancer among study males (adjusted OR = 1.36). If even an effect of active smoking remains largely obscured under study conditions, it is unlikely that an effect of ETS would be detected. Supporting these concerns are other recent studies in Xuanwei County that have confirmed widespread smoky coal use (e.g., 100% of households in Cheng Guan commune before 1958) and serious indoor air pollution with combustion byproducts, including mean indoor benzo[a]pyrene (BaP) levels of 9-15 ng/m³ in two communes using smoky coal during fall of 1983 (Mumford et al., 1987). Prior use of smoky coal at age 12 is associated with an OR of 3.7 for lung cancer in pair-matched female residents (Chapman et al., 1988). He et al. (1991), who report a strong association between indoor BaP and lung cancer, conclude that indoor air pollution appears to be the strongest risk factor for lung cancer in Xuanwei females.

Overall, this study makes important contributions to its principal objectives but is not helpful in assessing ETS and lung cancer. It is observed, for example, that persons in areas of Xuanwei with high lung cancer rates (and high smoky coal consumption) may inhale more BaP by spending 8 hours indoors than by smoking 20 cigarettes. Due to such factors, the authors observe, "the effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region therefore may not be applicable to other regions." Avoidance of areas atypically rich in competing exposures and careful control of potential confounders and interactive risk factors must be key objectives in studies of ETS and lung cancer.

A.4.25. PERS (Tier 1)

A.4.25.1. *Author's Abstract*

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a followup of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer that show the highest relative risks in smokers."

A.4.25.2. *Study Description*

This case-control study, undertaken to explore the role of passive smoking in lung cancer, is based on cohorts of Swedish women assembled prior to 1963. Nonsmokers were drawn from these cohorts to create matched case and control groups.

Cases are nonsmoking Swedish women included in the Swedish National Census or Twin Registry who responded to smoking status questionnaires in 1961-63 and who subsequently developed primary lung or bronchial cancer by 1980. Two control groups were cumulatively sampled from National Census or Twin Registry subjects who did not develop lung or bronchial cancer. In group 1, two controls were matched to each case on year of birth (± 1 year). In group 2, two controls were matched to each case (2:1) on year of birth (± 1 year) and vital status in 1980. Thus, there were 58 cases and 232 controls from the National Census and 34 cases and 136 controls from the Twin Registry. A followup questionnaire that included questions on spousal and parental smoking habits was distributed to each subject or the next of kin in 1984. Out of 92 cases of tracheal, bronchial, lung, or pleural cancer occurring by 1980, 15 cases in which a diagnosis of primary cancer of the lung or bronchus was not established were excluded. Exclusion of women indicated to be active smokers according to the 1984 questionnaire, or for whom ETS exposure information was not available, eliminated a further 10 cases. Active smoking and lack of exposure information eliminated 21 of the 368 controls initially assembled. Histological confirmation was available for 64 of the 77 cases with primary lung or bronchial cancer; 12 cases were cytologically confirmed, and the remaining case was verified at autopsy.

Never-smokers are subjects who report that they have never smoked any form of tobacco. A woman is ETS exposed if she has ever been married to a tobacco smoker; for women married more than once, only the longest marriage is considered. Exposure to spousal smoking is quantified in units of cigarettes per day or packs of pipe tobacco per week; parental smoke exposure is defined as 0, 1, 2, etc. (equal to the number of parents who smoke). No other sources of ETS exposure are considered. Never-smoking status was checked by comparing the responses to the 1961-63 questionnaires with those obtained in 1984. Data on sources of ETS were not checked. Never-married

women were classified as nonexposed to spousal smoke; widows and divorcees were classified according to the smoking status of the former husband with whom they had lived the longest. Of the never-smoking cases for whom passive smoking information was available, squamous and small cell tumors constituted 20 cases, 13 of whom were exposed to spousal smoke; of the other 47 cases, 20 were exposed to spousal smoke.

Responses to the ETS questionnaire were available for a total of 81 never-smoking cases and 347 never-smoking controls. The 67 cases with primary lung or bronchial cancer constitute the ETS study subjects. It is not clear how many of the 347 potential controls were employed in each analysis. Presumably many (up to 4 for each excluded case from the original 81 never-smoking cases) were not used in the matched analysis, whereas most or all were used in the unmatched analyses described subsequently.

A total of 33 of the 67 cases were exposed to spousal smoking. Among the never-smoking women, matched analyses indicate that the odds ratio for marriage to a smoker is 3.8 (95% C.I. = 1.1, 16.9) for squamous or small cell cancer compared with control group 1, 3.4 (0.8, 20.1) compared with control group 2, and 3.3 (1.1, 11.4) compared with both groups combined. For other cell types, corresponding odds ratios are 0.7, 0.8, and 0.8, respectively. Subsequent analyses abandoned matching and pooled all controls. For squamous and small cell cancer, high exposure to spousal smoking (15 or more cig./day or at least one pack of pipe tobacco/week for 30+ years) is associated with an age-adjusted odds ratio of 6.4 (1.1, 34.7), whereas the lower exposure is associated with an odds ratio of 1.8 (0.6, 5.3). The estimated odds ratios for other types of cancer are also elevated for the higher exposure, but not at the lower one. Odds ratios adjusted for age and spousal smoking when at least one parent smokes as well are above 1 (1.9; 95% C.I. = 0.5, 6.2) for squamous and small cell types but not for other types.

Logistic regression analyses reportedly produced the same results as did the stratified analyses. In addition, occupation, household radon, and urban or rural status had no significant effect. It is notable, however, that for all cancers combined, the odds ratio for radon exposure is 1.4 (0.4, 5.4), the odds ratio for spousal smoking is 1.2 (0.6, 2.6), and the odds ratio for radon and spousal smoking combined is 2.5 (0.8, 8.5). No separate analyses for squamous and small cell cancer are provided for radon and other potential confounders. The authors conclude that exposure to ETS is related primarily to the forms of lung cancer that show the highest relative risks in smokers. The results are internally consistent.

A.4.25.3. *Comments*

Although based on cohorts assembled for other purposes, this case-control study was specifically designed to investigate passive smoke exposure. Thus, all participants are ETS subjects that are matched. Matching criteria are rather modest--birthdate (± 1 year) for control group 1 and birthdate and vital status for control group 2. Because the study targeted all cases detected in the same cohorts from which matching controls were randomly drawn, good comparability of cases and controls is likely. No demographic comparisons of cases and controls for whom ETS information was available--and thus who constituted the analytical subjects--were provided to confirm this, however. Data on active smoking among subjects were collected both at the start and after the end of mortality monitoring,

providing an opportunity to verify the nonsmoking status over time and exclude individuals whose status had changed (apparently those reported in 1984 to have smoked daily for at least 2 years were so excluded). Thus, the probability of significant misclassification of active smoking status is low. Data on passive smoking were collected only after the end of mortality monitoring and by necessity employed proxy respondents extensively, so some misclassification of exposure is likely. Self-administration of questionnaires eliminates interviewer bias as a source of error, making misclassification less likely to be systematic, but preferential recall of smoke exposure by relatives of cancer victims could have produced a bias. Misclassification of disease is unlikely to have been a problem because most cases were histologically diagnosed and secondary lung cancers were excluded.

Consideration of spousal smoke exposure only in their longest marriage among women married more than once means that some of the unexposed group probably had substantial exposure to spousal smoking, creating a bias toward no association. Classification of all never-married women as unexposed despite possible smoking by cohabitants creates the same bias. Few subjects (less than 20%) were single, but the frequency of remarriage is unknown; therefore, it is unclear how important this bias might have been. Lack of consideration of workplace smoke exposure also may have contributed a bias toward the null hypothesis of no association.

The authors addressed a number of potential confounders and risk modifiers. Restriction of subjects to women eliminates potential effects of gender, and age is addressed by retaining age-matching or, alternatively, adjusting for age in all analyses. Reportedly neither occupation, radon, nor urban residence had significant confounding effects, which makes confounding by other factors related to socioeconomic status or lifestyle unlikely, too. An analysis of parental smoking controlled for spousal smoking. The authors do, however, present evidence that the odds ratio for simultaneous exposure to radon and spousal smoke approximately equals the sum of the separate odds ratios for radon and spousal smoke, consistent with additivity of the effects. But, perhaps due to limited numbers, they report results only for all cancers combined rather than for the squamous and small cell subgroup in which the only *significant* spousal smoking association was observed.

In summary, this study reports a consistent, dose-related, and (for high exposure levels) statistically significant positive association between exposure to spousal tobacco smoke and squamous and small cell carcinoma of the lung; a positive but nonsignificant association was also observed for parental smoke exposure. No significant associations were observed for other cell types. The observed associations apparently are not due to confounding by other major risk factors, although dietary and smoking habits were not directly addressed. A possible recall bias cannot be ruled out but seems unlikely given the negative results obtained for cancers other than squamous and small cell. The study provides a useful contribution to investigation of the relationship between ETS exposure and lung cancer.

A.4.26. SHIM (Tier 2)

A.4.26.1. *Author's Abstract*

"A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated RR of lung cancer was observed for passive smoking from mother (RR = 4.0; $p < 0.05$) and from husband's father (RR = 3.2; $p < 0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR = 4.8; $p < 0.05$). No appreciable differences in food intakes were observed between cases and controls."

A.4.26.2. *Study Description*

This study was undertaken in Nagoya, Japan, during 1982-85 to investigate the significance of passive smoking and other factors such as occupational history, domestic heating system, and dietary habits in the etiology of lung cancer in nonsmoking Japanese women. All data were collected specifically for this study, which was limited to never-smokers.

All subjects were obtained from four hospitals in Nagoya. Cases are women with primary lung cancer (of any type) treated in these hospitals between August 1982 and July 1985 who reported themselves to be never-smokers and consented to interview. Controls are women with a diagnosis other than lung cancer from the same or adjacent wards with controls matched 2:1 with cases on age (± 1 year), hospital, and date of admission. Cases were not restricted to incident disease, but controls were essentially density-sampled by admission date. Data collection was by self-administered questionnaire; no attempt at blinding is described. Of 118 female lung cancer cases treated during the study period, 4 refused to participate in the study and 24 were excluded as current or former smokers. Only a single matching control could be found for 17 of the cases. No other information on loss of potential controls is provided. There is a total of 90 (163) cases (controls), with 52 (91) currently married to a smoker. Cases and controls share identical age ranges (35-81 years) and have nearly identical mean ages (59 years for cases, 58 for controls). All cases were histologically diagnosed, excluding secondary lung cancers.

All study subjects are self-reported never-smokers. A number of individual sources of ETS in the home are considered, including smoking by mother, father, husband, father-in-law, mother-in-law, offspring, and siblings. For each of these sources, smoking in the home at any time constituted exposure. Workplace exposure was characterized simply as presence or absence; for other exposures, the number of cigarettes per day was obtained. In addition, data on length of marriage, time spent in the same room as the wife, and total number of cigarettes smoked were obtained for husbands. Exposure data were not checked, and marital status was not considered in the design or analysis of the study. The predominant type of lung cancer is adenocarcinoma (69 of 90 cases), followed by squamous (13), large cell (4), small cell (3), and adenoid cystic carcinoma (1). No data on airway proximity are provided.

Logistic regression was used to estimate the relative risk for each source of ETS exposure. No significant association with lung cancer was noted for smoking by the husband (RR = 1.1), father (RR = 1.1), husband's mother (RR = 0.8), offspring (RR = 0.8), or siblings (RR = 0.8); smoking by the subject's mother (RR = 4.0) and by the husband's father (RR = 3.2), however, are significant ($p < 0.05$). None of eight dietary factors, including green-yellow vegetable and fruit intake, demonstrated a significant association, nor did type of cooking fuel or frequency of cooking oil use. Occupational history of exposure to iron or other metals shows a moderately strong but nonsignificant association (RR = 2.8), whereas for use of kerosene, coal, or charcoal heating there is a mild association (RR = 1.6-1.7).

Simultaneous stratification by father-in-law's and mother's smoking indicates that the effects of the two exposures are not additive. Smoking by father-in-law, smoking by mother, and occupational metal exposure were included simultaneously in a logistic regression model. After adjusting the effect of each variable for the other two, the relative risk for maternal smoking, father-in-law's smoking, and metal exposure are 2.1, 3.2 ($p < 0.05$), and 2.4, respectively. The authors conclude that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. Because the precise situation of passive smoking in the home or other places is still unclear, however, the authors find that further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

A.4.26.3. Comments

This study employs a moderate number of well-matched cases and controls. Their comparability appears good, as supported by the identical age ranges and similar mean age and occupational categories for the two groups. A further strength of the study is its lack of reliance on proxy information with attendant potential for inaccurate recall. Exposure information was obtained from self-administered questionnaires, which eliminates the possibility of interviewer bias but may lead to inaccuracy due to misinterpretation of questions or varying care in their completion. Such problems with exposure information would tend to mask any actual association. Lung cancer was histologically diagnosed in all subjects and secondary lung cancers excluded, so diagnostic accuracy appears good for cases. Control diagnoses, however, were not validated, so some smoking-related disorders (in addition to the heart conditions noted in 3% of controls) may be included among the controls, a problem that once again would tend to reduce any observed association.

Restriction of subjects to never-smokers maximizes efficiency because effects of passive smoking would likely be dwarfed by active smoking. But it is unclear precisely what subjects were asked about their smoking status. Were any cut-points regarding past history, duration, or intensity specified? Thus, some misclassification of smoking status may have occurred, and if a greater proportion of persons with smoking family members misreport themselves to be never-smokers, this would create an upward bias.

The authors restrict their assessment of exposure from relatives to at-home smoking, which should be more meaningful than total smoking as a potential source of passive smoke exposure. Furthermore, they collected data on

smoking habits of all relatives, not just spouses or parents, thus reducing the chance of missing an exposure source. On the other hand, there is no consideration of total household smoking (all sources combined), cumulative exposure (except for husbands), or of pipe or cigar smoking; nor is there differentiation of current and former exposure--all potential sources of exposure misclassification, which would tend to make an association more difficult to detect.

Of the several sources of ETS exposure at home, only the relative risks for smoking by the mother and by the father-in-law are suggestive, and both of these are significant ($p < 0.05$). When these sources are considered simultaneously, however, and the effect of each is adjusted for the other, smoking by the husband's father remains significant ($RR = 3.2$; $p < 0.05$) but the effect of mother's smoking is diminished ($RR = 2.1$) and is not statistically significant. Exposure from the father-in-law is, of course, in adulthood. There is no evidence of an effect from husband's smoking ($RR = 1.1$), however, and these exposure sources were considered simultaneously so that the effect of one could be adjusted for the other. The large number of comparisons (e.g., eight groupings of passive smoke exposure, alternative spousal exposure measures, several occupational factors, and eight dietary factors) increases the likelihood that an observed relative risk will appear to be significant by chance alone (the effect of multiple comparisons).

Another aspect of the statistical analysis worth noting is that, although cases and controls appear well matched on age, hospital, and hospital admission date, these factors are not included in an adjusted analysis of the data (aside from the example with three sources of exposure described above). Consequently, some bias due to these factors is a possibility, although the demographic similarities between cases and controls makes a large effect unlikely.

In summary, this study presents some interesting results. It finds a strong (adjusted $RR = 3.2$) and statistically significant association between father-in-law's smoking at home and lung cancer and associations for maternal smoking and occupational metal exposure as well. The lack of association for any of the other sources of ETS examined could be due to problems with exposure assessment and control disease criteria. Equally, however, given the unclear treatment of matching factors in the analysis and the number of variables explored, the few substantial associations noted might be due to chance, confounding, or both. Were potential confounders clearly treated in their analyses, this study would have made a stronger contribution. As it stands, the study's data are of moderate utility, providing the number of comparisons and limitations regarding bias are kept in mind.

A.4.27. SOBU (Tier 2)

A.4.27.1. *Author's Abstract*

"A hospital-based case-control study among nonsmoking women was conducted to clarify risk factors in nonsmoking females in Japan. Cases consisted of 144 nonsmoking female lung cancer patients, and these were compared to 713 nonsmoking female controls. The odds ratios (95% confidence interval) for use of wood or straw as cooking fuels when subjects were 30 years old was estimated as 1.77 (1.08, 2.91). For those whose household members, other than husbands, had smoked, the odds ratio was estimated as 1.50 (1.01, 2.32). For those whose

mothers had smoked, the odds ratio was estimated as 1.28 (0.71, 2.31). Use of heating appliances did not show an elevated risk. Some points to be noted in this study of low-risk agents for lung cancer are discussed."

A.4.27.2. Study Description

This study was conducted in Osaka, Japan, to clarify risk factors for lung cancer in nonsmoking females in Japan. Of interest are the roles of both active and passive smoking and other indoor air pollutants, particularly smoke or fumes from sources of indoor cooking and heating. This article reports only on female nonsmokers in the study, which is not matched on any variables. A very similar article presenting interim results and using slightly fewer subjects than the one described here is by Sobue and coworkers (1990).

Cases consist of all newly admitted lung cancer patients in eight Osaka hospitals between January 1986 and December 1988. Controls were collected from newly admitted patients in one or two other wards of the same hospitals during that period. Almost 90% of the controls were admitted as cancer patients, about half of whom were diagnosed with breast cancer. Self-administered questionnaires designed for this study were completed by both cases and controls at the time of hospital admission. Cases are incident, and control sampling is density, unmatched aside from the time of hospital admission (within 1.5 years). The entire study, including active smokers and males, consists of 295 (1,079) female (male) cases and 1,073 (1,369) female (male) controls. Nonsmoking females compose 156 cases, of which there was missing information on 12. The resultant number of ETS subjects is 144 (731) female nonsmoking cases (controls). The age distribution of the cases (controls) is as follows: 40 to 49, 20 (238); 50 to 59, 34 (229); 60 to 69, 41 (186); and 70 to 79, 34 (78). The corresponding percentages are 14 (33), 34 (31), 28 (25), and 24 (11), which indicates that controls tend to be younger than cases. Also, the mean age of cases (controls) is 60 (56). There was no systematic review of histological diagnosis. All original diagnoses were confirmed microscopically, however, and all the pathologists involved in the eight participating hospitals were experienced specialists in lung cancer. Thus, the likelihood of secondary lung cancers among the cases should be small.

Several sources of ETS exposure are included, all of which occur in the home. Exposure in adulthood is expressed by two measures--smoking by the husband and other household members (the last category consists chiefly of households where the husband's father and/or sons smoke). Three sources of exposure in childhood are considered--father smokes, mother smokes, and other household members smoke. No information is provided on how exposure to spousal smoking is handled for unmarried women (single, divorced, or separated). The entire complement of cases and controls is included in the summary data for each of the five sources of exposure given above. If only married women were included in the study, no mention of it was found.

The histological data for ETS subjects are not classified by exposure to ETS, but the percentage of cases by cell type are given: squamous cell (8), small cell (5), adenocarcinoma (78), large cell (5), and other (4). The ETS data on spousal smoking consists of 80 of 144 (exposed/total) cases and 395 of 731 controls, for an odds ratio of 1.13 (95% C.I. = 0.78, 1.63). (Our calculations give 1.06 [0.74, 1.52].) The odds ratio for ETS exposure from other household members in adulthood is 1.57 (95% C.I. = 1.07, 2.31). (Our calculated values are 1.77 [1.21, 2.58].) For

ETS exposure in childhood by the father, mother, and by other household members, the respective odds ratios are 0.79 (95% C.I. = 0.52, 1.21), 1.33 (95% C.I. = 0.74, 2.37), and 1.18 (95% C.I. = 0.76, 1.84). Tests were conducted by the Mantel-Haenszel procedure, with stratification by age and education (two levels). Analysis by logistic regression, adjusted for age at time of hospitalization, was conducted for two of the exposure measures described above with similar outcomes. Based on this evidence, the author concludes that for childhood exposure, a slight increase of risk was suggested for those with smoking mothers, although statistical significance was not observed. For exposure in adulthood, an elevated risk was estimated for those with smoking household members other than husbands.

The statistical analysis includes exposure to sources other than ETS, namely, the use of wood or straw as cooking fuel, the use of heating equipment that pollutes the room with combustion products, and the use of charcoal foot warmers. All exposures considered, including ETS, are smoke or fumes from products burned indoors. It is concluded that significantly elevated risks were observed for subjects who had used wood or straw as cooking fuels at 30 years of age (OR = 1.89; 95% C.I. = 1.16, 3.06). No elevated risks were found for sources of indoor heating (use of kerosene, gas, coal, charcoal, and wood stoves without chimneys). Similarly, no significance was found for the use of charcoal foot warmers, a practice that was popular until the 1960s.

A.4.27.3. *Comments*

With 144 cases and 731 controls, the sample size is larger than many of the other case-control studies on ETS. Information on cases and controls was obtained by self-administered questionnaire, which is generally considered less reliable than face-to-face interviews. The questionnaires were presumably completed by the subjects themselves in all cases, however, which is preferable to proxy-supplied information. The information supplied was not verified from other sources, as noted by the authors in reference to testing for biomarkers of exposure to tobacco smoke (they note that laboratory tests can only detect recent exposure, but they could still be useful in eliminating current smokers who may misreport themselves as never-smokers). Although cases and controls were newly diagnosed patients within a short time period in the eight participating hospitals and were supplied with the same questionnaire, there are still some questions regarding the comparability of cases and controls and their representativeness of the target population.

Controls tend to be younger than cases: While mean ages are 56 and 60, respectively, 33% of controls, compared with 14% of cases, are below the age of 40. Controls also tend to be more educated than cases, with 69% of controls having completed 10 or more years of education compared to 52% of cases. Differences in age and educational level further reflect differences in lifestyle and socioeconomic status that may affect risk of disease. Also, the controls are predominantly cancer patients too, almost half with breast cancer, suggesting that the controls may be a biased sample (as noted by the authors). On the other hand, exclusion of breast cancer controls reportedly leaves the results unchanged. Furthermore, the statistical analysis stratifies on age and education, so even though cases and controls were not strictly matched on these variables, the reported results should not be due to confounding by either of these factors.

Although some of the issues and reservations described above are methodological in nature and apply to the study throughout, others are specific to the ETS data alone. For example, one might expect a question regarding the use of cooking with wood or straw at age 15 and at age 30 to be open to little subjective interpretation or error in recall, presuming that methods of cooking persisted for several years between changes within a household. Although there is some suggestive evidence of increased lung cancer from ETS exposure, the statistical evidence may be stronger for an association between lung cancer and use of wood or straw for cooking at age 30. Further support is provided by the observation that among those who had used wood or straw for cooking at age 30, 90% had also used those fuels at age 15, suggesting extended exposure in most cases. The age distribution of those exposed to wood or straw cooking is not given, but exposure at 30 years of age and before would allow for the long latency expected for lung cancer because 86% of the patients are at least 50 years of age.

The smoke from cooking sources may obscure or distort any impact of ETS exposure because the two sources probably contain some of the same carcinogens. The temporal dimension of exposure also may be a factor because indoor smoke from cooking may be less common at present than 30 years ago in comparison to ETS exposure. Further statistical analysis to adjust the effect of ETS exposure for the presence of smoke from cooking might aid interpretation of the results in this study.

A.4.28. STOC

A.4.28.1. *Author's Abstract*

(Note: This study has not been published. Only the abstract is available, which is given below.)

"Risk factors for lung cancer among women who had never smoked cigarettes were examined in an ongoing, population-based, case-control study conducted in Florida. One hundred and twenty-four primary carcinomas of the lung and 241 control women who had never smoked were included. Results suggest that childhood and adult exposures to environmental tobacco smoke may increase the risk of lung cancer among women who never smoked cigarettes. Having a husband who smoked cigarettes resulted in a statistically significant increase in risk of lung cancer among women who had never smoked, with an odds ratio of 1.8 (95% C.I. 1.1, 2.9). A 40% increase in risk was observed among women with less than 25 years of exposure to a spouse who smoked, when compared with women who reported their spouse had never smoked, with the risk increasing to 60% among women exposed 25 years or longer.

When exposure to tobacco smoke in childhood was considered, the data were less consistent. Having a parent who had smoked during the respondent's childhood did not increase the risk of lung cancer. However, among those respondents with high levels of exposure to parental smoking, an excess risk, although not statistically significant, was observed. Never-smoking women who accumulated 25 or more exposure years experience a 70% increase in risk (OR = 1.7, 95% C.I. 0.8, 3.6) of lung cancer compared with women who reported neither parent had smoked cigarettes."

A.4.29. SVEN (Tier 2)

A.4.29.1. *Author's Abstract*

"In a population-based case-control study, the association between female lung cancer and some possible etiological agents was investigated: 210 incident cases in Stockholm County, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative cancer risk was found for all histologic subgroups. Relative risk for those who had smoked daily during at least 1 year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose-response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have relative implications for risk assessments regarding passive smoking."

A.4.29.2. *Study Description*

This study was undertaken in Stockholm County, Sweden, from 1983 to 1986 to investigate the association between female lung cancer and some possible etiologic agents, particularly active and passive smoking. Because active smoking was an exposure of interest, cases and controls were not matched on smoking status; thus, the ETS study population is unmatched.

Cases are Swedish-speaking women with primary lung cancer from three Stockholm County hospitals who were willing and able to be interviewed between September 1983 and December 1985. Cases with carcinoid tumors were excluded from the ETS analysis. Both population and hospital-based control groups were assembled. Population controls were women randomly selected from the county population register, matched to a case on birthdate and interviewed between September 1983 and December 1986. Hospital controls were subjects originally interviewed as potential lung cancer cases but subsequently diagnosed with nonmalignant conditions. Population controls were enlisted and interviewed as soon as a case's diagnosis was confirmed, but because this confirmation took as long as a year after the interview, controls were not density sampled. Unblinded interviews were conducted face-to-face with all cases (and hospital controls) and 58% of the total population controls; the remainder were interviewed by telephone.

After exclusion of 21 potential cases due to initial diagnostic uncertainty, refusal, or illness precluding interview, 210 confirmed cases remained. Elimination of 172 ever-smokers and four subjects with carcinoid or not-microscopically-confirmed tumors left 34 never-smoking cases. Similarly, 209 population and 191 hospital controls were included in the total study, but a combined total of only 174 were never-smokers. The total case population averaged 62.5 years of age, but no other demographic information regarding cases or controls is provided. All cases used in the ETS analyses were histologically or cytologically confirmed primary lung cancers.

Daily smoking for at least 1 year is the criterion for a smoker; all other persons are considered never-smokers. Pipe and cigar smoking are never specifically addressed. Exposure to ETS is calculated for four sources: mother, father, home, and work. Having a smoking mother or father (at any time during ages 0-9 years) constitutes exposure to that particular source, whereas the presence of a smoker at home and work constitutes exposure. Adulthood and total lifetime exposure are considered separately for home and workplace exposure. Exposure levels are arbitrarily scored 1 for nonexposure, 2 for exposure to one source, and 3 for exposure to both sources in trend analyses of never-smokers, where exposures are considered in pairs (i.e., maternal and paternal smoking, home and workplace exposure). No other units of ETS exposure are used. Adenocarcinomas constituted 22, squamous cell 5, and small cell 2 of the 34 lung cancers occurring among never-smokers in the ETS population; no further histologic details regarding the ETS study population are provided.

To maximize available case numbers, parental smoking was first analyzed among all cases and community controls using stratification to adjust for active smoking (cig./day) and age. A risk of 1.8 (95% C.I. = 0.5, 7.0) was estimated for maternal smoking and 0.8 (0.3, 1.4) for paternal smoking. A trend analysis in which maternal, paternal only, and no parental smoke exposure were scored as 3, 2, and 1, respectively, revealed no indication of trend ($p = 0.9$). Analyses restricted to never-smokers used both community and hospital-based controls combined. Among cases (controls), for childhood up through 9 years of age, 3 (5) had smoking mothers, 12 (71) had smoking fathers (but not mothers), and 19 (98) were unexposed. This yielded an age-adjusted risk estimate of 3.3 for maternal smoking (with or without paternal smoking) and 0.9 for paternal smoking during childhood. Adult exposure at home *and* at work yielded an estimated risk of 2.1, whereas exposure at home *or* work yielded a risk of 1.2. For lifetime exposure, the estimated risks for exposure as both a child *and* adult and as either a child *or* an adult were 1.9 and 1.4, respectively. None of these associations were statistically significant, and no significant trends were observed. The authors conclude that the results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity, which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking.

A.4.29.3. Comments

This study was undertaken to explore the role of active as well as passive smoking in lung cancer. After exclusion of active smokers, the available number of cases is too small to yield much statistical power.

Cases and population-based controls were initially matched on date of birth, but this matching was abandoned in the ETS analysis; furthermore, unmatched hospital-based controls are combined with the population-based controls in most analyses to boost available numbers. The comparability of these groups is thus unclear, and the authors provide no demographic comparisons to facilitate assessment of this potential problem. The reported similarity of results using only population-based controls is reassuring, but no details are provided as to *how* similar results actually were.

Diagnostic misclassification of cases is unlikely, given the histological or cytological confirmation of all cases and exclusion of secondary cancers. All cases were interviewed face-to-face, but 42% of controls were interviewed by telephone. The accuracy of responses may thus be lower for controls than for cases. In addition, because interviews were not conducted blindly, inflation of estimated associations through interview bias is possible. A potential bias is also introduced by the rather large amount of active smoking required for classification as an ever-smoker. This allows considerable active smoking among persons in the never-smoker group, the effect of which could mask an effect of passive exposure, or, if co-varying positively with passive smoking, cause overestimation of association.

The first set of analyses of paternal and maternal smoking includes ever-smokers while attempting to adjust for active smoking on the basis of average daily cigarette consumption. The adequacy of this adjustment is questionable given the large estimated risks associated with active smoking relative to those posited for passive smoking, so the elevated estimated risks for maternal smoking obtained in these analyses are of questionable validity.

Restriction of the analyses to never-smokers similarly produces an elevated odds ratio for maternal smoking of 3.3, but the numbers involved (three cases and five controls) are so small that this value is quite unstable. A pattern of increasing estimated risk with increasing sources of exposure (at home or at work) as an adult and increasing periods of exposure (in childhood or adulthood) over the lifetime is suggestive of an association between lung cancer and ETS, but again small numbers preclude statistical significance of these results.

Restriction of the study population to females rules out the possibility of a gender-related effect. The likelihood of an ethnicity effect is reduced by restriction to Swedish-speaking residents of Stockholm County, and age is reportedly controlled for in all analyses. No other potential risk modifiers are addressed. For example, marital status is not considered in the analyses of spousal smoking, leaving open the possibility that nonsmoking-related differences between married and unmarried women contributed to the observed association. The reported similarity of results when only population controls were used instead of hospital and population controls combined provides a general argument against bias due to source of controls, although no specifics regarding the degree of similarity were supplied.

In summary, this study presents consistent evidence of associations between lung cancer and maternal, home, and workplace passive smoking exposure. Limited numbers preclude statistical significance, and interviewer bias or effects due to dietary or other factors cannot be ruled out as contributors to the observed results. Bearing these limitations in mind, the study's results are inconclusive but (excluding the analyses that include active smokers) do make a useful contribution to the pool of information available regarding ETS and lung cancer.

A.4.30. TRIC (Tier 3)

A.4.30.1. *Author's Abstract*

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were

nonsmokers. Among the nonsmoking women, there was a statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

A.4.30.2. Study Description

This study was undertaken in Athens, Greece, to investigate the relationship of spousal smoking and lung cancer. All female Caucasian Athenian residents admitted to one of three chest or cancer hospitals in Athens and assigned a final diagnosis of lung cancer other than adenocarcinoma and alveolar carcinoma from September 1978 through June 1980 were interviewed by a physician. Controls were gathered from nonsmoking female Caucasian Athenian patients hospitalized during the same time period in the Athens Orthopedic Hospital. Some prevalent cases were thus presumably included, so control sampling probably approximated a density approach but did not strictly conform to one.

Diagnostic information was obtained from patients' charts. Exposure information was obtained by face-to-face unblinded interviews conducted by the same physician for all subjects. A total of 51 cases and 163 controls were interviewed. Of these, 11 cases and 14 controls reported themselves to be active smokers, leaving 40 cases and 149 controls as ETS subjects. No interview refusals are reported. Mean age of cases (controls) is 62.8 (62.3) years. Husband's education was marginally higher in controls than cases, with 63% and 58% of spouses having completed primary school, respectively. No other demographic comparisons are reported for the ETS subjects alone. For the sample population including smokers, factors such as age, duration of marriage, occupation, education, and urban versus rural residence are all similar for cases and controls, except once again educational level is slightly higher for controls. There is no indication that verification of diagnosis or exclusion of secondary lung cancers was undertaken in cases. Of the 51 total cases, 14 were diagnosed histologically, 19 cytologically, and 18 by radiological or clinical means. No breakdown is given for the ETS subjects alone.

The study classifies as nonsmokers both reported never-smokers and former smokers who quit more than 20 years ago. It is not mentioned whether cigar and pipe smoking are considered as sources of exposure. Nonsmoking women are considered exposed to ETS if they are married to a man classified as a smoker. The average number of cigarettes smoked per day by the husband and the number of years of marriage are used to estimate the total number of cigarettes smoked by the husband during marriage. No data on childhood or nonspousal ETS exposure were collected. Single women are grouped with women married to a nonsmoker and are thus considered unexposed. Widowed or divorced women were classified according to their former husband's smoking status on the assumption that smoking stopped at death or divorce. No checks of exposure information are reported.

For ETS subjects, the number of cases (controls) exposed over the total is 29 to 40 (78/149). The crude odds ratio calculated by the reviewers is 2.4 (95% C.I. = 1.12, 5.16). The results presented in the article are all stratified by

level of husband's smoking. The odds ratios are 1.8, 2.4, and 3.4 when the husband is a former smoker, smokes 1 to 20 cigarettes per day, and smokes 20 or more cigarettes per day, respectively. No confidence intervals are given, but a test for upward trend was statistically significant ($p < 0.02$). When ETS exposure is estimated by total number of cigarettes smoked during marriage, odds ratios (1.3, 2.5, and 3.0) increase with cumulative exposure (1-99, 100-299, and 300+ thousand, respectively). The upward trend remains statistically significant at $p < 0.02$. No analyses adjusted for age or other factors. With regard to age and other demographic variables, the authors conclude from the similarity of cases and controls that it is not necessary to stratify for these variables in the analysis, particularly because none is significantly associated with smoking in the study.

The authors note that this study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected if passive smoking is related to lung cancer, and the outcome is unlikely to be due to chance. Other limitations noted include the high percentage (35%) of cases lacking cytology and the selection of controls from a hospital different from those of the cases; it is argued, however, that neither of these appears to be consequential. The observation is made that it is potentially easier to detect an effect of passive smoking in the Greek population than in most Western populations, because in the latter groups, the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, would tend to confound and conceal the lesser effects of passive smoking.

A.4.30.3. Addendum

In a letter to the editor of *Lancet* in 1983, Trichopoulos et al. released a data table derived from extension of subject collection through December 1982. This nearly doubled the sample size used in the 1981 publication, yielding 77 nonsmoking cases (102 total) and 225 smoking controls (251 total). The crude odds ratio calculated by the reviewers is 2.08 (95% C.I. = 1.20, 3.59). The results for the expanded study show very little change; (estimated) relative risks when husbands are former smokers (1-20 cig./day and > 20 cig./day) compared with nonsmokers are 1.95, 1.95, and 2.54, respectively. The test for upward trend in the dose-response is significant ($p = 0.01$). No other analyses are presented.

A.4.30.4. Comments

This study was conceived and undertaken to explore the association of spousal smoking with lung cancer and does not rely on a preexisting data set. Thus, the investigators were in a position to design their selection and data collection to maximize the strength of their findings. This did not, however, prevent the appearance of some design and analytical flaws.

Demographics of the total case and control populations are very similar. All subjects in the spousal smoking analysis are resident Athenian nonsmoking women hospitalized in the same area of Athens; case and control groups have very similar mean ages, and their husbands are comparable in education. Thus, the groups probably have good

demographic comparability, although it would have been helpful if the detailed demographic comparisons were focused on the nonsmokers alone. Most of the controls (108 out of 163) were being treated for fractures, a relatively minor and nonchronic illness compared with lung cancer, which may make them more representative of the general community than of hospitalized patients as a whole. This should reduce the problem of inclusion of smoking-related illnesses in the control group.

Although the researchers sought to exclude adenocarcinomas and alveolar carcinomas, presumably considering these would be less smoking related, nearly two-thirds of the cases were not histologically confirmed, so an indeterminate number of these cell types was probably included. More important, the infrequency of histologic confirmation and lack of mechanisms to verify diagnoses or primary tumor status introduces potential for misclassification. The likely effect is a bias toward no association.

The researchers clearly devoted considerable thought to the smoking and exposure criteria, particularly with regard to changes in smoking and marital status over time. Single women were, however, automatically classified as unexposed. The authors contend that this is warranted by the traditional nature of Greek society and report that analyses restricted to married women result in similar, and still statistically significant, associations, although with somewhat lower estimated risks. There is a small reduction in the odds ratios after exclusion of single women, however, and the restriction of the full analyses and results to married women may have been useful.

Another issue related to exposure concerns inclusion of former smokers in the study, provided they had not smoked for at least 20 years. Active smoking 20 to 30 years before the onset of lung cancer may be of etiological relevance, however, in view of a long latency period for lung cancer. Although use of the same interviewing physician for all subjects eliminates the problem of interobserver variability, it leaves open the potential problem of interviewer bias in exposure assessment, presumably toward a positive association, because the interviews were apparently conducted unblinded (virtually unavoidable with regard to diagnosis, given that controls were drawn from orthopedic trauma and rheumatology wards).

A larger concern, however, is the potential effect of risk factors or modifiers not addressed in the analysis. The authors contend that the similar distribution of demographic variables between cases and controls eliminates the need to consider these variables in the analyses, but adjusting for relevant variables is recommended even in a matched study (see Section 5.4.1). More convincing is the contention that these variables were not significantly associated with smoking in these data, although no specifics are included. The appearance of a statistically significant trend for ETS exposure measured by either current spousal smoking or cumulative cigarette consumption during marriage lends further support to an association between spousal smoking and increased lung cancer incidence. Potential factors such as diet, cooking, and heating practices, however, are not addressed.

Overall, the issues addressed above would probably produce a conservative bias, resulting in an underestimate of the degree of association. The study's basic design is sound. It provides statistically significant evidence of dose-response, and although the limitations described above should be borne in mind, it provides useful data for assessment of the relationship between ETS and lung cancer.

A.4.31. WU (Tier 2)

A.4.31.1. *Author's Abstract*

"A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated RRs for ADC were observed for passive smoke exposure from spouse(s) (RR = 1.2; 95% C.I. = 0.5, 3.3) and at work (RR = 1.3; 95% C.I. = 0.5, 3.3). Childhood pneumonia (RR = 2.7; 95% C.I. = 1.1, 6.7) and childhood exposure to coal burning (RR = 2.3; 95% C.I. = 1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β -carotene foods but not for total preformed vitamin A foods and vitamin supplements."

A.4.31.2. *Study Description*

This study was undertaken in California during 1981 and 1982 to investigate the role of smoking and other factors in the etiology of lung cancer in women. These other factors included prior lung disease, coal heating and cooking, diet, and occupation. Both active and passive smokers are included; some of the ETS analyses retain active smokers while attempting to adjust for smoking status.

Cases are white female English-speaking Los Angeles County residents under 76 years of age at time of diagnosis with primary adenocarcinoma or squamous cell cancer of the lung between April 1, 1981, and August 31, 1982. Cases are restricted to U.S.-, Canadian-, or European-born individuals with no history of prior cancer other than nonmelanoma skin cancer. Controls are density sampled, matched individually on neighborhood and age (± 5 years), and meet all case criteria (except, of course, diagnosis of lung cancer). The L.A. County tumor registry was used to identify incident cases for inclusion in the study, whereas controls were recruited house to house. Interviews to obtain exposure data were conducted by telephone with participating subjects, apparently unblinded.

A total of 490 eligible cases were identified; 270 were not interviewed because they were too ill or had died (190), their physician refused permission to contact them (28), they could not be located (8), or they refused (44). Those not interviewed did not differ significantly from those interviewed with regard to age or their marital, religious, or smoking status as recorded on registry records. Refusals eliminated 70 potential controls. The case and control populations had nearly identical mean ages for adenocarcinoma, 59.7 versus 59.5 years, respectively, and for squamous cell cancer, 61.4 versus 61.1 years, respectively. No other demographics are provided. Histologic diagnoses were obtained for all cases.

For spousal smoking, exposure constitutes having a spouse who smoked while living with the subject. For workplace smoke, exposure is based on the opinion of the subject. It is not clear whether for the lung cancer analyses, parental smoking refers only to adult life (as for spousal and workplace exposure) or to the childhood and teen years (as was stipulated for coal and preadult lung disease exposures). Adult life seems most probable. Units of exposure

for spousal and parental smoking are cigarettes per day and years of exposure, apparently entered into a regression model as a combined variable; for occupational exposure, units are in years of exposure. Exposure data were apparently not checked, treatment of cigar and pipe smoking is never mentioned, and no results are reported for household smoking aside from spouse and parents, although information on this exposure was collected. Never-married women were excluded from the spousal smoking analysis, but marital status was not otherwise considered in the analyses. The only histologic or airway proximity information provided for the ETS subjects is that 29 adenocarcinomas occurred among nonsmokers, 12 of which were bronchoalveolar.

The total study population includes 220 cases and an equal number of matched controls. Of the cases, 149 are adenocarcinoma and 71 are squamous cell. Nonsmokers constituted 29 of the adenocarcinoma cases and 62 of the corresponding controls, while composing 2 of the squamous cell cases and 30 of the controls. No raw data are presented regarding passive smoking and lung cancer. Logistic regression analysis of matched pairs was used in all calculations. Results restricted to nonsmokers are presented only for adenocarcinoma. An estimated relative risk of 1.2 is found for spousal smoking, 1.3 for workplace exposure, and 0.6 for smoking by either parent. None of these estimates was statistically significant. Exposure from spouses and at work, however, shows a dose-response trend with years of exposure, yielding estimated relative risks of 1.0, 1.2, and 2.0, for 0, 1 to 30, and 30 or more years of exposure, respectively.

Analyses that include active smokers but attempt to adjust for them by including the number of cigarettes smoked per day and age at start of smoking in a logistic regression model are presented for both lung cancer types. For adenocarcinoma, estimated relative risks for maternal, paternal, spousal, and workplace exposure of 1.7, 1.3, 1.2, and 1.2, respectively, were obtained. For squamous cell cancer, maternal, paternal, spousal, and workplace relative risks are 0.2, 0.9, 1.0, and 2.3, respectively. None of these estimates is statistically significant.

History of lung disease at least 5 years prior to diagnosis of lung cancer reportedly had no significant association with lung cancer. History of lung diseases before age 16 yielded a significant association for pneumonia (RR = 2.7 [95% C.I. = 1.1, 6.7] for adenocarcinoma and RR = 2.9 [95% C.I. = 0.5, 17.4] for squamous cell cancer) but not for six other diseases.

Heating or cooking with coal during the childhood and teenage years is also significantly associated with lung cancer (RR = 2.3 [95% C.I. = 1.0, 5.5] for adenocarcinoma and RR = 1.9 [95% C.I. = 0.5, 6.5] for squamous cell). Among dietary factors, low beta carotene consumption is significantly associated with adenocarcinoma (RR = 2.7) and mildly associated with squamous cell (RR = 1.5). Diets low in dairy products and eggs have similar relative risk values. No significant associations were noted for vitamin A consumption, occupation, or other health history factors not previously considered.

The authors conclude that the etiology of squamous cell carcinoma can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the adenocarcinoma cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of

adenocarcinoma cases. Passive smoking and vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

A.4.31.3. *Comments*

This study took particular care with its treatment of case and control assembly. Extensive inclusion criteria extending to both groups, matching not only on age but neighborhood of residence, and retention of matching through analysis all bode well for comparability of cases and controls. The virtually identical mean ages of cases and controls indicate the success of these efforts. In addition, exclusive use of incident cases reduces the potential for selection bias, and density sampling of controls reduces potential problems with temporal variation. The only real fault in the treatment of cases and controls is the failure to provide any demographic comparison other than for age, thus denying concrete confirmation of the expected high case-control comparability.

Case diagnoses are likely to be accurate, because all were histologically diagnosed, making misclassification unlikely and making cell-type-specific analyses possible. Although no one pathologist or team verified these determinations, the authors note that there is generally good interobserver agreement for the cell types included in this study. Potentially eligible cases not interviewed due to illness, refusal, or other reasons did not differ significantly in demographic or smoking status from those actually interviewed, again arguing against biased selection.

No proxy interviews were used, and all subjects were English-speakers, enhancing the chances of obtaining accurate exposure information. On the other hand, interviews were by telephone--possibly decreasing accuracy relative to face-to-face interviewing--and apparently unblinded, thus introducing possible interviewer bias toward positive results.

Collection of exposure data seems generally adequate, except that treatment of pipe and cigar smokers is not described. This is coupled with an uncertain definition of parental smoking and lack of treatment of household smokers other than parents or spouses in the analyses, despite collection of data on this point. These uncertainties probably translate into nondifferential exposure misclassification, biasing results toward the null.

The analyses suffer from the common problem of restricted numbers of nonsmoking cases--29 for adenocarcinoma and only 2 for squamous cell. Some factors examined are restricted to nonsmokers alone for adenocarcinoma, but for most analyses, an adjustment for active smoking by logistic regression modeling was attempted. The adequacy of such adjustment may be questionable. For adenocarcinoma, however, the results for passive smoking were very similar, regardless of whether restriction or adjustment was used. Further, a dose-response pattern was seen for cumulative years of spousal and workplace exposure among nonsmokers. The results of the analyses for squamous cell are too unstable to be meaningful, given the paucity of cases.

The findings of substantial associations between lung cancer (or, at least, adenocarcinoma) and childhood pneumonia and coal burning are of interest. It must be borne in mind that seven adult respiratory diseases (including pneumonia) as well as six other childhood respiratory diseases were examined, so the possibility that the pneumonia association was an artifact of multiple comparisons cannot be ruled out. History of hysterectomy and multiparity

showed nearly significant associations with adenocarcinoma, but it is not clear how many other health history factors also were considered. Coal burning has been associated with lung cancer in several other studies. Similarly, as in several other studies, one found an association with low beta carotene intake, but there was no evidence of a dose-response gradient, and no significant association was found for preformed vitamin A. The strongest association with a dietary factor was actually that for low intake of dairy products and eggs, which showed a consistent dose-response pattern. The use of a matched-pair analytical approach controls for effects of age or neighborhood, which also reduces the likelihood of neighborhood-related factors such as socioeconomic status as major sources of bias. Confounding due to active smoking can be ruled out in the passive smoking results for adenocarcinoma and is not likely in regard to other factors given adjustment for this variable in all analyses. Likewise, the authors report that adjustment for childhood pneumonia, coal burning, and beta carotene intake did not alter their results. Strangely, however, no adjustment for dairy product and egg intake--the dietary factor with the most convincing association with lung cancer in their data--was carried out.

Overall, this study's results are consistent with a mild association between spousal and workplace ETS exposures and lung adenocarcinoma, although they support no such association for parental smoking. In addition, the study raises childhood pneumonia, coal burning during early life, low intakes of beta carotene, and low intake of dairy products and eggs as potential moderate risk factors that should be considered by future studies. The results for squamous cell carcinoma are uncertain given the small number of nonsmoking cases available, and in all instances, they lack statistical significance due to sample size limitations. Thus, the study provides useful information on the relationship of adenocarcinoma of the lung with ETS and a number of other factors; information regarding squamous cell cancer is of less utility for the objectives of this report.

A.4.32. WUWI (Tier 4)

A.4.32.1. *Author's Abstract*

"A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities that have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumors among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to Kang and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of

lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung."

A.4.32.2. Study Description

The objective of this study was to evaluate the role of potential risk factors for lung cancer in Harbin and Shenyang, two cities among those with the highest mortality rate for lung cancer in China. Active smokers are included in the cases, so data on ETS subjects constitute a subset of the whole study.

Cases consist of female residents under age 70 newly diagnosed with primary lung cancer in about 70 participating hospitals in Harbin and Shenyang between 1985 and 1987. Controls are female residents randomly selected from the general population of these cities and frequency matched by 5-year age group to the age distribution of female lung cancer cases reported in the cities in 1983. Trained interviewers collected information on smoking habits, diet, cooking and heating practices, and other factors from subjects in face-to-face unblinded interviews.

A total of 1,049 qualifying cases were found, including both ever-smokers and never-smokers, of which 405 were diagnosed by histology, 309 by cytology, and 351 by radiology or clinical means. (*Note:* These diagnostic numbers do not total 1,049. The 351 figure may be intended to be 251, which would give a total of 965 diagnoses, about the number of cases interviewed.) Of these, 85 either died prior to interview, refused to participate, or could not be located. Mean age of participating cases was 55.9 years, whereas that of the 959 controls was 55.4 years. Nonsmokers compose 417 of the interviewed cases and 602 of the controls.

A smoker is defined as a person who has smoked cigarettes for 6 months or longer, so a nonsmoker apparently may have smoked for up to 6 months. Information on all types of tobacco products smoked was collected. Sources of ETS exposure include smoking by any household cohabitant and smoking by individuals (spouse, mother, and father) over the course of the subject's lifetime. Exposure at the workplace is also addressed. ETS exposure in the home is expressed in terms of cigarettes per day and number of years smoked; no units of measurement are used for workplace smoking. No checks on exposure data were undertaken. Marital status of subjects is not discussed. Of the cases with histological or cytological data, adenocarcinomas compose 310 (41.7%), squamous cell cancers 201 (28.9%), small and oat cell cancers 117 (16.8%), and large cell or unspecified types 66 (9.5%). No data on airway proximity or diagnostic breakdowns limited to nonsmokers are provided.

Statistical analyses of potential risk factors, including ETS, largely include data on active smokers and then adjust for the effect due to smoking by logistic regression, along with other potential confounders such as age, education, and location (Shenyang vs. Harbin). These analyses indicate no increase in risk from household sources of ETS, with estimated relative risks of 0.8 (household cohabitants), 0.9 (spouse), 1.0 (mother), and 1.0 (father). The estimated risk for workplace exposure is nonsignificant (RR = 1.2). Restriction of analyses to ETS subjects alone (i.e., only the nonsmokers) produced similar results, with estimated relative risks of 0.7 for general cohabitant, 0.7 for spouse, 0.9 for mother, 1.1 for father, and 1.1 for workplace exposure. The ETS exposure from spousal smoking is

significantly low (i.e., associated with a decrease in lung cancer by this analysis, as apparent from the confidence interval; RR = 0.7; 95% C.I. = 0.6, 0.9).

The smoking-adjusted analyses indicate associations with lung cancer for several types of heating devices, including kangas (brick beds heated by pipes from the stove or by burners directly underneath), coal stoves, and heated brick walls or floors. The risk associated with the use of burning kangas (those heated by stoves underneath) shows an upward trend with years of use, becoming statistically significant at 21 or more years of use (RR = 1.5; 95% C.I. = 1.1, 2.0). Significantly elevated risks are also associated with use of heated brick walls or floors (RR = 1.5 [1.1, 2.1] for 1-20 years of use; RR = 1.4 [1.1, 1.9] for > 20 years). Nonsignificant increases in risk are noted for use of kangas of all types, coal stoves, and coal burners; nonsignificant reductions in risk are indicated for noncoal stoves and central heat. Deep-frying cooking at least twice a month and eye irritation during cooking are both significantly associated with lung cancer, as are regular intake of animal protein and fresh fruit. (*Note:* Multiple comparisons may be a factor for the apparent significance of some items, as discussed further in the next section.)

The authors find no overall association between lung cancer and ETS exposure. On the other hand, coal burning, exposure to cooking oil fumes, and chronic lung disease all may be risk factors. Consumption of beta carotene shows no evidence of a protective effect. Overall, active smoking is the major cause of lung cancer among women in the regions sampled.

A.4.32.3. Comments

The sample size is impressive, with ETS exposure data available for nearly 1,000 cases including smokers and more than 400 cases when restricted to nonsmokers, thus providing substantial statistical power. All subjects are women recruited from two industrial cities in northeast China, reducing potential for complications due to regional or urban-rural differences. Nearly all of the hospitals in these cities were involved, all cases occurring in these hospitals were targeted, and the rate of participation among eligible cases was high; thus potential for selection bias is minimized. The effective case recruitment in combination with the use of general population controls maximizes generalizability of the study's results for northeast China. It would have been useful, however, to present the results for the two component study locations separately. Although coordinated in planning and execution, there are two separate study locations, and the sources of heterogeneity between them tends to be obscured when results are combined.

Unfortunately, the study's results with regard to ETS are more limited than the strengths listed above might suggest. The inclusion of age, education, and city as control variables in all analyses is laudable, thus eliminating the possible influence of these factors. The attempt to control for potential sources of confounding that may be causally related to lung cancer by statistical methods, however, is less certain. Although some analysis was conducted with data for active smokers included, to the authors' credit they also analyzed data for ETS subjects alone (i.e., with the data for active smokers removed), which is the surest way to control for confounding by active smoking. Other potential causes of lung cancer (e.g., air pollution from coal-burning stoves, smokiness during cooking, and deep-fat

frying foods) also need to be taken into account in an analysis of ETS. This cannot always be accomplished effectively by statistical methods, particularly when there are multiple risk factors to be taken into account that are variable, poorly measured, and possibly more potent risk factors than ETS may be.

A case-control study is ideally designed and executed under conditions where cases and controls are as comparable as possible aside from the factor of interest, such as ETS exposure. The presence of other risk factors may tend to pollute and obscure, much like the contamination of a laboratory experiment. In this same sense, the presence of indoor sources of smoke other than ETS may contaminate an environment for measuring ETS effects because the non-ETS smoke likely contains many of the same carcinogens as ETS, and possibly in much larger quantities, depending on the relative levels of exposure. Other factors outside the home, such as workplace exposure to coal dust and to smoke from burning fuel that was reported more often in cases than controls, contribute to the potential confounding in a similar way. Consequently, a credible analysis of ETS requires being able to adjust for these likely confounding factors satisfactorily, and the ability to do that depends on precise measures of all exposures as well as the presence of substantial numbers of subjects for various exposure combinations. That kind of statistical analysis is not given in the article, and it does not appear to have been possible, based on conversations with the authors (Wu-Williams and Blot) and the text of the article: "Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognized as a cause of lung cancer around the world (U.S. DHHS, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighborhood air pollution (Xu et al., 1989)."

The potential rate of non-ETS sources of indoor air pollution, particularly coal combustion, appears exceptionally strong in the study area. For example, a case-control study of primary lung cancer in urban Shenyang residents aged 30-69 in 1985-87 reports that the age, education, and smoking-adjusted OR for kang use among women ranges from 1.9 to 3.4, the latter figure being for the higher exposure level (at least 50 years of use). Fully 44% of the controls and 55% of the cases are at the highest exposure level, and only 3% of controls and less than 1% of cases have no exposure. Benzo[a]pyrene levels in 30 homes sampled during the winter averaged 60 ng/m³, which is 60 times the U.S. recommended limit, and indoor measurements in single and two-story homes were even higher (Xu et al., 1989). Abstracts of two papers published in Chinese indicate that similar conditions exist in Harbin. Sun (1992) found a smoking-adjusted OR for soft coal use of 2.26 with a highly significant trend for duration of exposure among female residents. Also, Wang (1989) reports ORs of 10.6 for high coal consumption and 15.2 for "indoor smog pollution in winter" among females in Harbin. It is noted that winter levels of benzo[a]pyrene are 26.7 times higher in residents' bedrooms than outdoors, suggesting that indoor coal combustion may even be more of a problem in Harbin than Shenyang.

The multivariate analysis reported in the article reinforces the viewpoint that any ETS effect may be dominated by the presence of other risk factors. In that analysis, variables were allowed to enter a logistic regression model in the order of their explanatory value (a stepwise regression exercise in statistical terminology). The order of

entry into the model is deep frying, eye irritation, pneumonia, household tuberculosis, burning kang, self-reported occupational exposure to burning fuel, passive smoking, and heated brick wall or floor. Passive smoking, in this exercise, is significant ($p < 0.05$) but in the direction of reducing lung cancer, not contributing to it. The 0.05 value, however, is not fully meaningful as a significance level for ETS, because of the stepwise procedure used (the same data used in the construction of a model is used for testing variables in the model) and because of the likely confounding between ETS and other variables. Note, for example, that passive smoking entered the model ahead of heated brick wall or floor, which is highly significant when analyzed alone, whereas passive smoking is not.

The evidence for association of lung cancer with burning coal and deep-frying foods is particularly provocative, as it indicates two factors that may play a substantial role in the etiology of lung cancer in northeast China and, hence, in other areas as well where such practices occur. The associations noted with other factors are also of interest, but their importance is undermined by the problem of multiple comparisons. In the table presenting results for dietary factors, for example, 26 risk estimates are computed, 4 of which are significant at the 5% significance level (for a two-sided test, 2.5% level for the test of an effect), only one more significant finding than expected due to chance alone.

Being somewhat speculative, the use of cases age 70 and below may be a factor. Wells (1988) showed that about one-half of the female passive smoking deaths occur after age 70 for the studies included in that reference. If ETS is a risk for lung cancer and if individual susceptibility to lung cancer is a factor, some of the stronger risk factors such as coal burning and cooking oil may have caused lung cancer in the more susceptible subjects before passive smoking had a chance to exert itself.

In summary, this large and basically well-executed study observed no significant association between exposure to ETS from cohabitants, spouse, parents, or workplace and lung cancer. Lack of control for a number of other significant risk factors identified in the study undermines these results, however. The associations with coal burning for heat and oil frying are particularly notable. Use of the heating devices most strongly linked with lung cancer is presumably more common in colder northern regions, whereas stir-frying may be more widespread in Asian communities, without regard to climate. Thus, this study was exploratory, designed to generate hypotheses rather than to test the specific hypothesis that ETS exposure is associated with lung cancer. It identifies a number of potential risk factors for consideration in future studies. The prevalence of these factors in the study population combined with the lack of analysis of their association with ETS exposure, however, renders the results for ETS inconclusive.